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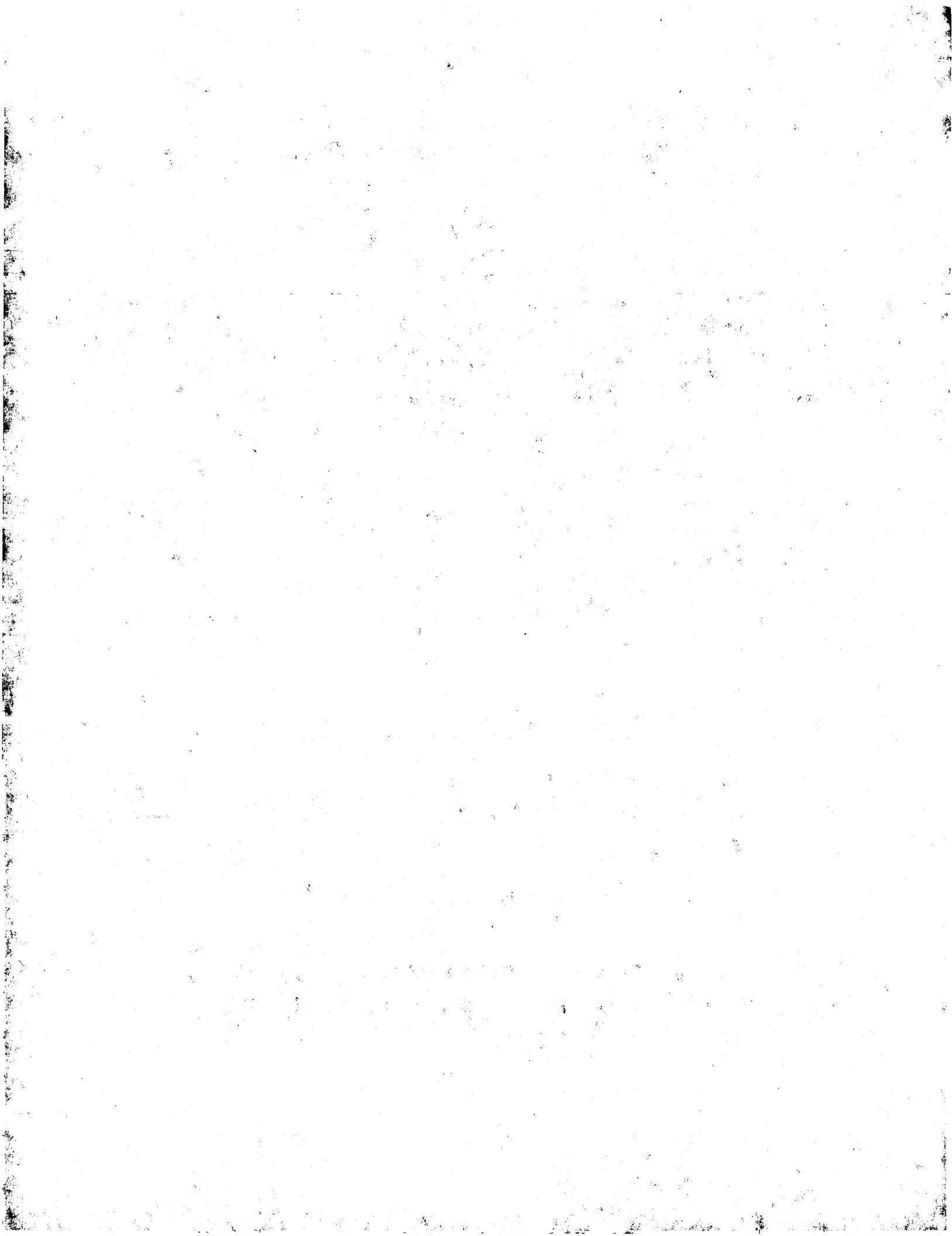
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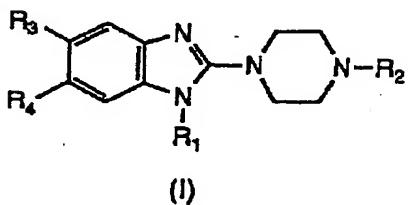


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(57) [abstract]

5 [constitution] A benzimidazole derivative of the formula
(I)



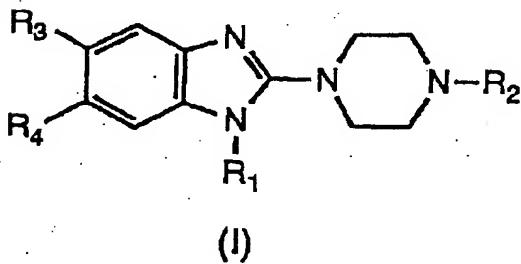
10 wherein R₁ is a lower alkyl group, a lower alkoxy (lower alkyl) group or a tetrahydrofurfuryl group, R₂ is a hydrogen atom, a methyl group or an amino group, R₃ is a halogen atom or a methyl group and R₄ is a hydrogen atom or an amino group, or a pharmacologically acceptable acid
15 addition salt thereof.

[effect] The above-mentioned novel benzimidazole derivative has a strong 5-HT₃ antagonistic action and is useful as an antiemetic drug.

20

[claim]

[claim 1] A benzimidazole derivative of the formula (I)



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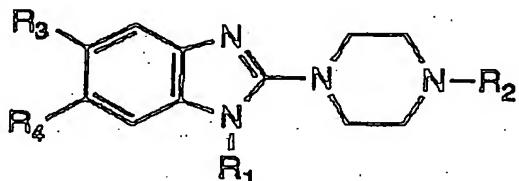
wherein R₁ is a lower alkyl group, a lower alkoxy (lower alkyl) group or a tetrahydrofurfuryl group, R₂ is a hydrogen atom, a methyl group or an amino group, R₃ is a halogen atom or a methyl group and R₄ is a hydrogen atom or an amino group, or a pharmacologically acceptable acid addition salt thereof.

[Detailed Description of the Invention]

[0001]

[Field of Industrial Utilization] The present invention relates to a novel benzimidazole derivative. More particularly, it relates to a benzimidazole derivative of the formula (I)

[0002]



15

(I)

wherein R₁ is a lower alkyl group, a lower alkoxy (lower alkyl) group or a tetrahydrofurfuryl group, R₂ is a hydrogen atom, a methyl group or an amino group, R₃ is a halogen atom or a methyl group and R₄ is a hydrogen atom or an amino group, or a pharmacologically acceptable acid addition salt thereof.

[0003] The novel benzimidazole derivative of the present invention has a strong serotonin antagonistic action and 25 is useful as an antiemetic drug.

[0004]

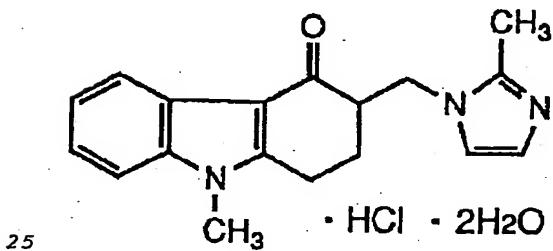
[Prior Art] In cancer treatment, chemotherapeutic agents such as cisplatin and the like are indispensable. At the same time, however, side effects such as vomition and the

like pose problems and make continuation of the treatment difficult.

[0005] In recent years, it has been clarified that the expression of said vomition relates to one of the serotonin [5-hydroxytryptamine (hereinafter to be referred to as 5-HT)] receptors. 5-HT is one of the neurotransmitters in the body, and as the receptors in which 5-HT is involved, 5-HT₁, 5-HT₂ and 5-HT₃ are generally known. Of these, 5-HT₃ receptor is responsible for the vomition caused by cancer chemotherapy. To be precise, administration of a chemotherapeutic agent releases 5-HT, the released 5-HT is bonded to a 5-HT₃ receptor in the abdominal region, which in turn stimulates, via the abdominal vagal nerve, chemoreceptor trigger zone present in the modullary fourth ventricle and then vomiting center, whereby vomition occurs.

[0006] It has been reported that ondansetron (GR38032F, see the formula below) having a 5-HT₃ antagonistic action, is effective for suppression of vomition caused by the administration of chemotherapeutic agents such as cisplatin and the like [Cancer. Chemother. Pharmacol., 23, 389-391 (1989)].

[0007]



[0008] Meanwhile, the application of a 2-piperazinylbenzimidazole derivative as a pharmaceutical agent has been already known. For example, JP-A-50-126682 discloses a 2-piperazinylbenzimidazole derivative having

an analgesic, anti-inflammatory action, reciting 1-methyl-2-(4-methyl-1-piperazinyl)benzimidazole (compound A), 2-(4-methyl-1-piperazinyl)benzimidazole (compound B) and the like as examples. In addition, JP-A-58-79983 recites, as 5 an example of benzimidazole derivative having an antihistaminic action, a compound having a lower alkoxy (lower alkyl) group at the 1-position of benzimidazole, such as 1-(2-ethoxyethyl)-2-(4-methyl-1-piperazinyl)benzimidazole 3/2 fumarate (compound C) and 10 the like. However, the 5-HT₃ antagonistic action of these 2-piperazinylbenzimidazole derivatives and an antiemetic action based thereon have not been known at all.

[0009]

[Problems to be Solved by the Invention] The present 15 inventors have conducted various studies with the aim of developing a pharmaceutical agent having a 5-HT₃ antagonistic action and effective for the suppression of vomiting caused by cancer chemotherapy using cisplatin and the like.

20 [0010] It is therefore an object of the present invention to provide a novel compound satisfying such demand.

[0011]

[Means of Solving the Problems] The present inventors have variously considered and found that a novel benzimidazole 25 derivative of the aforementioned formula (I) or a pharmacologically acceptable acid addition salt thereof satisfies such demand, which resulted in the completion of the present invention.

30 [0012] In the aforementioned formula (I), of the groups defined by R₁, the lower alkyl group is an alkyl group having 1 to 5 carbon atoms, which may be linear, branched or cyclic. Specific examples of the lower alkyl group include methyl group, ethyl group, propyl group, isopropyl group, cyclopropyl group, butyl group, 2-butyl group,

isobutyl group, 3-pentyl group, cyclopentyl group and the like. The lower alkoxy (lower alkyl) group is an alkyl group having 1 to 5 carbon atoms, which is substituted by alkoxy group having 1 to 5 carbon atoms. Specific examples of the lower alkoxy (lower alkyl) group include 2-ethoxyethyl group, 3-ethoxypropyl group and the like.

[0013] of the groups defined by R₃, halogen atom is exemplified by chlorine atom, fluorine atom and the like.

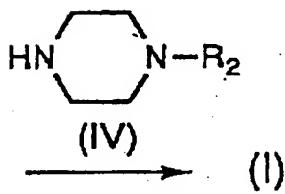
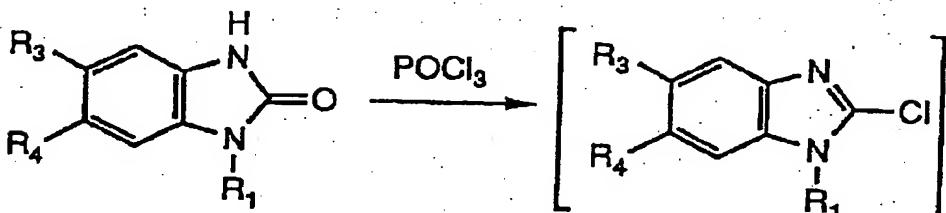
[0013] of the groups defined by R₃, halogen atom is exemplified by chlorine atom, fluorine atom and the like.

[0014] The compound of the present invention, which is represented by the aforementioned formula (I), can be produced by, for example, any of the following methods.

[0015] (Method A) Of the compounds of the formula (I), a compound wherein R₂ and/or R₄ are/is not amino group(s) (R₁ and R₃ are the same as the groups defined above) can be produced by the following method.

15 produced by the following method.

【0016】



20 wherein R₁, R₂, R₃ and R₄ are as defined above, except when
R₂ and/or R₄ are/is amino group(s).

To be specific, a compound of the formula (II) is reacted with generally 2-6 equivalents of phosphorus oxychloride relative to the compound of the formula (II).

without solvent or in an inert solvent such as chloroform and the like at 60°C to the boiling point of the solvent for 0.5 - 4 hrs to give compound (III). Then, without purification, this compound is reacted with generally 2-6 equivalents of a compound of the formula (IV) relative to the compound of the formula (III) without solvent or in an inert solvent such as xylene and the like at 80-160°C or the boiling point of the solvent for 1 - 4 hrs, whereby a compound of the above-mentioned formula (I), wherein R₂ and/or R₄ are/is not amino group(s) can be produced.

[0017] The compound of the formula (II) used as a starting material in the above-mentioned production method can be produced by a method according to the method described in, for example, the aforementioned JP-A-50-126682 (see

15 Production Examples below).

[0018] (Method B) Of the compounds of the formula (I), a compound wherein R₂ is an amino group and R₄ is a hydrogen atom (R₁ and R₃ are the same as the groups defined above) can be produced by reacting a compound of the formula (I), wherein R₂ and R₄ are both hydrogen atoms, which is obtained by the above-mentioned method A, with sodium nitrite in an acidic aqueous solution by a conventional method to give a compound wherein R₂ is a nitroso group, and then reducing the nitroso group with zinc and acetic acid and the like.

[0019] (Method C) Of the compounds of the formula (I), a compound wherein R₂ is a hydrogen atom or a methyl group and R₄ is an amino group (R₁ and R₃ are the same as the groups defined above) can be produced by reacting a compound of the formula (I) obtained by the above-mentioned method A, wherein R₂ is a hydrogen atom or a methyl group and R₄ is a hydrogen atom with fuming nitric acid in acetic acid, or by reacting the compound of the formula (I) with concentrated nitric acid in concentrated

sulfuric acid at -10 to 10°C to give a corresponding compound wherein R₄ is a nitro group, then reacting the obtained compound with a reducing agent generally in an amount of 4-7 equivalents without solvent or in an inert 5 solvent such as ethanol and the like from room temperature to the boiling point of the solvent for 0.1 - 10 hrs.

[0020] As the above-mentioned reducing agent, for example, zinc and hydrochloric acid, iron and hydrochloric acid, tin(II) chloride and hydrochloric acid and the like are 10 used.

[0021] (Method D) Of the compounds of the formula (I), a compound wherein R₂ and R₄ are both amino groups (R₁ and R₃ are the same as the groups defined above) can be produced by obtaining a compound of the formula (I) wherein R₂ is a 15 hydrogen atom and R₄ is a nitro group in the same manner as in the above-mentioned method C, then reacting the compound with sodium nitrite in an acidic aqueous solution by a conventional method to give a compound wherein R₂ is a nitroso group, reducing the nitro group in the same 20 manner as in the above-mentioned method C, and then reducing the nitroso group in the same manner as in the above-mentioned method B with zinc and acetic acid and the like.

[0022] Where necessary, the compound (I) of the present 25 invention can be converted to a pharmacologically acceptable acid addition salt according to a conventional method.

[0023] As the pharmacologically acceptable acid addition salt of the compound of the present invention, salts with 30 inorganic acids such as hydrochloric acid, sulfuric acid and the like, salts with organic acids such as maleic acid, fumaric acid and the like can be mentioned.

[0024]

[Action and Effect of the Invention] The compound of the

present invention shows a strong antagonistic action (5-HT₃ antagonistic action) on the Bezold-Jarisch reflex induced by 5-HT, as compared to ondansetron, which is a positive control compound, as shown in the following Test Examples. Accordingly, based on its strong 5-HT₃ antagonistic action, the compound of the present invention is useful as a suppressive agent of vomition caused by cancer chemotherapy using cisplatin and the like.

[0025] The action and effect of the compound of the present invention is explained in the following by referring to Test Examples.

[0026] **Test Example 1** 5-HT₃ antagonistic action:

[0027] [test compounds]

(1) Compounds of Examples 1-18 and 20-37 (the compounds of the present invention)

(2) 1-methyl-2-(4-methyl-1-piperazinyl)benzimidazole dimaleate (dimaleate of the aforementioned compound A)

(3) 2-(4-methyl-1-piperazinyl)benzimidazole (the aforementioned compound B)

(4) 1-(2-ethoxyethyl)-2-(4-methyl-1-piperazinyl)benzimidazole 3/2 fumarate (the above-mentioned compound C)

(5) ondansetron (positive control compound)

[0028] [test method] The 5-HT₃ antagonistic action was measured according to the method of Collins et al. [Br. J. Pharmacol., 80, 570P (1983)] using, as an index, antagonistic action on the Bezold-Jarisch reflex (reflexive bradycardia) induced by 5-HT.

[0029] That is, male S.D. rats (body weight 200-350 g) were anesthetized by intraperitoneal administration of urethane (1.25 mg/kg). Cannula was inserted into the carotid artery and the heart rate was measured. A test compound was dissolved in physiological saline or 5% ethanol in physiological saline and intravenously

administered (1 µg/kg, i.v.). Five minutes after the administration of the test compound, 5-HT was dissolved in physiological saline was intravenously administered (0.04 mg/kg, i.v.). The heart rate was measured and suppression 5 rate of reflexive bradycardia by the test compound was determined, based on which 5-HT₃ antagonistic action was expressed according to the evaluation criteria shown below.

[0030] Suppression rate: less than 20%;-, 20-50%;+, not less than 50%;++ Note that, of the test compounds, 10 ondansetron, which is a positive control compound, hardly showed the above-mentioned suppressive effect at 1 µg/kg i.v. Thus, the suppression rate at 3 µg/kg i.v. was also determined.

[0031] [test results] The results are shown in Table 1.
15 [0032] As is clear from Table 1, the compound of the present invention has a strong 5-HT₃ antagonistic action as compared to compounds A, B and C, as well as to ondansetron.

[0033]
20 [Table 1]

Table 1 5-HT₃ antagonistic action

Test compound (Ex. No.)	5-HT ₃ antagonistic action (1 µg/kg i.v.)	Test compound (Ex. No.)	5-HT ₃ antagonistic action (1 µg/kg i.v.)
1	++	2 3	++
2	++	2 4	++
3	++	2 5	++
4	++	2 6	++
5	++	2 7	+
6	++	2 8	++
7	++	2 9	++
8	++	3 0	++
9	+	3 1	++
1 0	+	3 2	++
1 1	++	3 3	++
1 2	++	3 4	++
1 3	++	3 5	++
1 4	++	3 6	++
1 5	++	3 7	++
1 6	++	Compound A	—
1 7	++		
1 8	+		
2 0	++	Compound B	—
2 1	++		
2 2	++		
		Compound C	—
		ondansetron	- (+ *)

*: 3 µg/kg i.v.

[0034]

[Examples] The present invention is explained in more detail in the following by referring to Production Examples and Examples.

- 5 [0035] Production Example 1 5-chloro-1-ethyl-2-benzimidazolone: (1) 2,5-Dichloronitrobenzene (25 g) was added to ethylamine (35 g) and the mixture was stirred in a sealed tube at 110°C for 3.5 hrs. After cooling, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was concentrated and the precipitated crystals were collected by filtration to give 21 g of 4-chloro-N-ethyl-2-nitroaniline (mp 90.5-93.0°C).
- 10 [0036] (2) 4-Chloro-N-ethyl-2-nitroaniline (21 g) was dissolved in ethanol (100 ml). Thereto was added 2.5N aqueous sodium hydroxide solution (25 ml). Under reflux, zinc powder (23 g) was added by small portions and the mixture was stirred for 10 min. Insoluble material was filtered off and water was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 17 g of 2-amino-4-chloro-N-ethylaniline (mp 62.0-64.0°C).
- 15 [0037] (3) 2-Amino-4-chloro-N-ethylaniline (14 g) and urea (20 g) were stirred at 160°C for 10 hrs. After cooling, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 15 g of 5-chloro-1-ethyl-2-benzimidazolone. This was partially taken and recrystallized from acetonitrile. The resulting crystals

showed the following property values.

[0038] mp 170.0-172.0°C NMR (CDCl_3 , δ ppm):
1.27(3H,t), 3.84(2H,q), 6.65-7.15(3H,m). Elemental analysis
for $\text{C}_9\text{H}_9\text{ClN}_2\text{O}$: Calculated (%) C, 54.97; H, 4.61; N, 14.25 Found
5 (%) C, 55.09; H, 4.58; N, 14.38 According to the method of
Production Example 1, a compound of the formula (II)
(wherein R₄ is a hydrogen atom) was produced, which is
shown in Table 2.

[0039]

10 [Table 2]

Table 2 (No. 1)

No	R ₁	R ₃	mp (°C)	NMR (δ ppm) [solvent]	Elemental analysis (%) [molecular formula]		
					Calculated (found)		
C	H	N					
1	methyl	C1	226.0 -228.0	[CDCl ₃]: 3.32 (3H, s), 6.76- 7.36 (3H, m), 10.86 (1H, brs).	[C ₈ H ₇ ClN ₂ O] 52.62 3.86 15.34 (52.53 4.04 15.41)		
2	propyl	C1	182.0 -184.0	[DMSO-d ₆]: 0.89 (3H, t), 1. 22-2.15 (2H, m), 3.74 (2H, t), 6.55-7.35 (3H, m), 10.97 (1H, brs).	[C ₁₀ H ₁₁ ClN ₂ O] 57.02 5.26 13.30 (56.86 5.25 13.39)		
3	cyclo- propyl	C1	213.5 -214.5	[CDCl ₃]: 0.60-1.56 (4H, m), 2.46-3.16 (1H, m), 6.70-7. 39 (3H, m) 10.54 (1H, brs).	[C ₁₀ H ₉ ClN ₂ O] 57.57 4.35 13.43 (57.37 4.51 13.39)		
4	butyl	C1	141.0 -143.0	[CDCl ₃]: 0.70-2.40 (7H, m), 3.87 (2H, t), 6.66-7.53 (3H, m), 10.73 (1H, brs).	[C ₁₁ H ₁₃ ClN ₂ O] 58.80 5.83 12.47 (59.00 5.81 12.32)		
5	tetra- hydro- furyl	C1	157.0 -158.5	[CDCl ₃]: 1.35-2.35 (4H, m), 3.45-4.65 (5H, m), 6.78-7. 39, (3H, m), 10.53 (1H, brs).	[C ₁₂ H ₁₃ ClN ₂ O ₂] 57.04 5.19 11.09 (56.95 5.20 11.10)		
6	2-butyl	C1	140.0 -142.0	[CDCl ₃]: 0.87 (3H, t), 1.52 (3H, d), 1.67-2.47 (2H, m), 4.04-4.82 (1H, m), 6.77-7. 37, (3H, m), 11.04 (1H, brs).	[C ₁₁ H ₁₃ ClN ₂ O] 58.80 5.83 12.47 (58.72 5.81 12.58)		

[0040]

[Table 3]

Table 2 (No. 2)

No	R_1	R_3	mp (°C)	NMR (δ ppm) [solvent]	Elemental analysis (%) [molecular formula] Calculated (found)		
					C	H	N
7	iso-butyl	C1	145.0 -153.0	[CDCl ₃]: 0. 98(6H, d), 1. 72- 2. 72(1H, m), 3. 65(2H, d), 6. 68-7. 43(3H, m), 10. 97(1H, brs).	[C ₁₁ H ₁₃ C ₁ N ₂ O] 58. 80 5. 83 12. 47 (58. 81 5. 74 12. 47)		
8	3-pentyl	C1	147.0 -148.0	[CDCl ₃]: 0. 84(6H, t), 1. 37- 2. 45(4H, m), 3. 87-4. 57(1H, m), 6. 80-7. 37(3H, m), 11. 19 (1H, brs).	[C ₁₂ H ₁₅ C ₁ N ₂ O] 60. 38 6. 33 11. 74 (60. 31 6. 25 11. 82)		
9	cyclopentyl	C1	156.0 -158.0	[CDCl ₃]: 1. 20-2. 70(8H, m), 4. 50-5. 35(1H, m), 6. 78-7. 60 (3H, m), 10. 95(1H, brs).	[C ₁₂ H ₁₃ C ₁ N ₂ O] 60. 89 5. 54 11. 83 (61. 15 5. 60 12. 04)		
10	3-ethoxypropyl	C1	100.5 -102.0	[CDCl ₃]: 1. 22(3H, t), 1. 70- 2. 45(2H, m), 3. 15-3. 75(4H, m), 3. 99(2H, t), 6. 75-7. 45 (3H, m), 10. 80(1H, brs).	[C ₁₂ H ₁₅ C ₁ N ₂ O ₂] 56. 59 5. 94 11. 00 (56. 80 5. 89 11. 06)		
11	butyl	CH ₃	128.0 -131.0	[DMSO-d ₆]: 0. 31-1. 91(7H, m), 2. 28(3H, s), 3. 68(2H, t), 6. 41-7. 10(3H, m), 10. 63(1H, brs).	[C ₁₂ H ₁₆ N ₂ O] 70. 56 7. 89 13. 71 (70. 37 7. 77 13. 56)		
12	iso-butyl	CH ₃	123.0 -125.0	[CDCl ₃]: 0. 98(6H, d), 1. 89- 2. 82(1H, m), 2. 37(3H, s), 3. 70(2H, d), 6. 72-7. 32(3H, m), 10. 83(1H, brs).	[C ₁₂ H ₁₆ N ₂ O] 70. 56 7. 89 13. 71 (70. 41 8. 07 13. 80)		

【0041】

【Table 4】

No	R_1	R_3	mp (°C)	NMR (δ ppm) [solvent]	Elemental analysis (%)		
					[molecular formula]		
				Calculated (found)	C	H	N
13	3-ethoxy-propyl	CH ₃	123.0 -125.5	[CDCl ₃]: 1. 21(3H, t), 1. 68-2. 35(2H, m), 2. 35(3H, s), 3. 08-3. 78(4H, m), 4. 00(2H, t), 6. 58-7. 43(3H, m), 10. 75(1H, brs).	[C ₁₃ H ₁₈ N ₂ O ₂] 66. 64 7. 74 11. 96 (66. 49 7. 87 12. 15)		
14	butyl	F	111.0 -112.0	[CDCl ₃]: 0. 57-2. 17(7H, m), 3. 86(2H, t), 6. 52-7. 22(3H, m), 10. 75(1H, brs).	[C ₁₁ H ₁₃ FN ₂ O] 63. 45 6. 29 13. 45 (63. 54 6. 43 13. 42)		
15	2-ethoxy-ethyl	Cl	131.0 -133.0	[CDCl ₃]: 1. 11(3H, t), 3. 43(2H, q), 3. 51-4. 18(4H, m), 6. 78-7. 22(3H, m), 10. 95(1H, brs)	[C ₁₁ H ₁₃ ClN ₂ O ₂] 54. 98 5. 44 11. 64 (55. 27 5. 50 11. 69)		
16	cyclopentyl	CH ₃	147.0 -150.0	[CDCl ₃]: 1. 17-2. 67(8H, m), 2. 34(3H, s), 4. 42-5. 27(1H, m), 6. 62-7. 24(3H, m), 10. 72(1H, brs).	[C ₁₃ H ₁₆ N ₂ O ₂ •1/2H ₂ O] 69. 31 7. 61 12. 43 (69. 27 7. 52 12. 41)		

5 [0042] Production Example 2 5-chloro-1-isopropyl-6-nitro-2-(1-piperazinyl)benzimidazole: (1) 2,5-Dichloronitrobenzene (150 g) was added to isopropylamine (150 g) and the mixture was stirred in a sealed tube at

100°C for 4 hrs. After cooling, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried over anhydrous magnesium sulfate. The solvent 5 was evaporated under reduced pressure to give 163 g of 4-chloro-N-isopropyl-2-nitroaniline (mp 72.0-74.0°C).

[0043] (2) 4-Chloro-N-isopropyl-2-nitroaniline (8 g) was dissolved in ethanol (20 ml). Zinc powder (9.8 g) was added and concentrated hydrochloric acid (20 ml) was added 10 by small portions. To the mixture was added aqueous ammonia for neutralization, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The 15 residue was distilled (bp 90°C/0.4 mmHg) to give 4.2 g of 2-amino-4-chloro-N-isopropylaniline (mp 35.0-36.0°C).

[0044] (3) 2-Amino-4-chloro-N-isopropylaniline (14 g) and urea (15 g) were stirred at 160°C for 3.5 hrs. After cooling, water was added to the reaction mixture and the 20 mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid, aqueous sodium hydroxide solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. Isopropyl alcohol was 25 added to the residue and the resulting crystals were collected by filtration and recrystallized from acetonitrile to give 7 g of 5-chloro-1-isopropyl-2-benzimidazolone (mp 183.0-186.0°C).

[0045] (4) 5-Chloro-1-isopropyl-2-benzimidazolone (4.0 g) 30 was dissolved in o-dichlorobenzene (80 ml) and 70% nitric acid (2.0 g) was added dropwise. The mixture was stirred at 60°C for 1 hr and allowed to cool. The precipitated crystals were collected by filtration. The crystals were washed with diethyl ether and water to give 4.1 g of 5-

chloro-1-isopropyl-6-nitro-2-benzimidazolone (mp 270.0-272.0°C).

[0046] (5) Ethylene carbonate (0.7 g) and phosphorus oxychloride (1.1 ml) were added to 5-chloro-1-isopropyl-6-nitro-2-benzimidazolone (1.0 g) and the mixture was refluxed for 5 hrs. Phosphorus oxychloride was evaporated under reduced pressure and the residue was dissolved in ethyl acetate and poured into ice water. Aqueous sodium hydroxide solution was added for neutralization. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 0.9 g of 2,5-dichloro-1-isopropyl-6-nitrobenzimidazole (mp 150.5-152.5°C).

[0047] (6) 2,5-Dichloro-1-isopropyl-6-nitrobenzimidazole (4.6 g) and piperazine (14.6 g) were added to toluene (50 ml) and the mixture was refluxed for 30 min. Water was added to the reaction mixture and then hydrochloric acid was added to acidify the aqueous layer. The aqueous layer was alkalified with aqueous sodium hydroxide solution and the precipitated crystals were collected by filtration to give 4.2 g of 5-chloro-1-isopropyl-6-nitro-2-(1-piperazinyl)benzimidazole. This was partially taken and recrystallized from ethanol. The resulting crystals showed the following property values.

[0048] mp 179.0-180.0°C NMR (CDCl_3 , δ ppm): 1.65(6H,d), 1.82(1H,s), 2.95-3.65(8H,m), 4.37-5.10(1H,m), 7.77(1H,s), 8.17(1H,s). Elemental analysis for $\text{C}_{14}\text{H}_{18}\text{ClN}_5\text{O}_2$: Calculated (%) C, 51.93; H, 5.60; N, 21.63 Found (%) C, 52.00; H, 5.68; N, 21.75

[0049] Example 1 5-chloro-1-ethyl-2-(4-methyl-1-piperazinyl)benzimidazole: 5-Chloro-1-ethyl-2-benzimidazolone (see Production Example 1) (2.1 g) was refluxed in phosphorus oxychloride (5 ml) for 1 hr. After allowing to cool, the reaction mixture was poured into ice

water and extracted with chloroform. The chloroform layer was washed with aqueous sodium hydroxide solution and water, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 2.5 g of crude 2,5-dichloro-1-ethylbenzimidazole. Then, the obtained crude 2,5-dichloro-1-ethylbenzimidazole (1.5 g) and N-methylpiperazine (3.0 g) were added to xylene (5 ml) and the mixture was refluxed for 2.5 hrs. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was applied to silica gel chromatography [eluted with a mixed solvent of chloroform:methanol=10:1] and recrystallized from acetonitrile to give 0.9 g of the title compound.

[0050] mp 124.0-125.5°C NMR (CDCl₃, δ ppm): 1.40(3H,t), 2.35(3H,s), 2.40-2.73(4H,m), 3.11-3.50(4H,m), 3.99(2H,q), 7.0-7.6(3H,m). Elemental analysis for C₁₄H₁₉ClN₄: Calculated (%)C, 60.32; H, 6.87; N, 20.10 Found (%C, 60.34; H, 6.87; N, 20.03

[0051] Example 2 5-chloro-1-methyl-2-(4-methyl-1-piperazinyl)benzimidazole: In the same manner as in Example 1 except that 5-chloro-1-methyl-2-benzimidazolone (see Production Example 1, compound No. 1, Table 2) was used instead of 5-chloro-1-ethyl-2-benzimidazolone, the title compound was obtained.

[0052] mp 139.0-141.0°C NMR(CDCl₃, δ ppm): 2.39(3H,s), 2.52-2.96(4H,m), 3.17-3.56(4H,m), 3.59(3H,s), 6.87-7.87(3H,m). Elemental analysis for C₁₃H₁₇ClN₄: Calculated (%)C, 58.98; H, 6.47; N, 21.16 Found (%C, 58.90; H, 6.38; N, 21.06

[0053] Example 3 5-chloro-2-(4-methyl-1-piperazinyl)-1-propylbenzimidazole: In the same manner as in Example 1

except that 5-chloro-1-propyl-2-benzimidazolone (see Production Example 1, compound No. 2, Table 2) was used instead of 5-chloro-1-ethyl-2-benzimidazolone, the title compound was obtained, though recrystallized from
5 isopropyl ether.

[0054] mp 89.0-91.0°C NMR (CDCl_3 , δ ppm): 0.92(3H,t), 1.45-
2.10(2H,m), 2.36(3H,s), 2.45-2.85(4H,m), 3.18-3.57
(4H,m), 3.93(2H,t), 7.02-7.73(3H,m). Elemental analysis for
 $\text{C}_{15}\text{H}_{21}\text{ClN}_4$: Calculated (%) C, 61.53; H, 7.23; N, 19.13 Found
10 (%) C, 61.37; H, 7.13; N, 19.26

[0055] Example 4 5-chloro-1-cyclopropyl-2-(4-methyl-1-piperazinyl)benzimidazole: In the same manner as in Example 1 except that 5-chloro-1-cyclopropyl-2-benzimidazolone (see Production Example 1, compound No. 3, 15 Table 2) was used instead of 5-chloro-1-ethyl-2-benzimidazolone, the title compound was obtained, though recrystallized from isopropyl alcohol.

[0056] mp 105.5-106.5°C NMR (CDCl_3 , δ ppm): 0.90-
1.40(4H,m), 2.37(3H,s), 2.46-2.87(4H,m), 2.87-3.35
20 (1H,m), 3.35-3.82(4H,m), 6.90-7.65(3H,m). Elemental analysis for $\text{C}_{15}\text{H}_{19}\text{ClN}_4$: Calculated (%) C, 61.96; H, 6.59; N, 19.27 Found (%) C, 62.02; H, 6.61; N, 19.18

[0057] Example 5 1-butyl-5-chloro-2-(4-methyl-1-piperazinyl)benzimidazole · 3/2 fumarate: 1-Butyl-5-chloro-2-benzimidazolone (see Production Example 1, compound No. 4, Table 2) (5.0 g) was refluxed in phosphorus oxychloride (7 ml) for 2 hrs. After allowing to cool, the reaction mixture was poured into ice water and extracted with chloroform. The chloroform layer was washed with aqueous sodium hydroxide solution and water, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 4.5 g of crude 1-butyl-2,5-dichlorobenzimidazole. Then, the obtained crude 1-butyl-2,5-dichlorobenzimidazole (3.0 g) and N-methylpiperazine
30

(5.0 g) were added to xylene (5 ml), and the mixture was refluxed for 3 hrs. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was applied to silica gel chromatography [eluted with a mixed solvent of chloroform:methanol=10:1] to give 1.2 g of 1-butyl-5-chloro-2-(4-methyl-1-piperazinyl)benzimidazole.

Then, ethanol (10 ml) was added to fumaric acid (0.8 g), and the mixture was heated for dissolution. This solution was poured into 1-butyl-5-chloro-2-(4-methyl-1-piperazinyl)benzimidazole (1.2 g). After cooling, the precipitated crystals were collected by filtration, and the obtained crystals were recrystallized from a mixed solvent of ethyl acetate-ethanol to give the title compound (0.9 g).

[0058] mp 167.0-169.0°C NMR ($\text{CDCl}_3\text{-DMSO-d}_6$, δ ppm): 0.58-2.10(7H,m), 2.45(3H,s), 2.61-3.00(4H,m), 3.03-3.61(4H,m), 4.01(2H,t), 6.71(3H,s), 7.04-7.50(3H,m), 9.65(3H,brs).

Elemental analysis for $\text{C}_{16}\text{H}_{23}\text{ClN}_4 \cdot 3/2\text{C}_4\text{H}_4\text{O}_4$: Calculated (%): C, 54.94; H, 6.08; N, 11.65 Found (%): C, 54.82; H, 5.90; N, 11.62

[0059] Example 6: 1-butyl-5-chloro-2-(1-piperazinyl)benzimidazole: 1-Butyl-5-chloro-2-benzimidazolone (see Production Example 1, compound No. 4, Table 2) (10.0 g) was refluxed in phosphorus oxychloride (20 ml) for 1 hr. After allowing to cool, the reaction mixture was poured into ice water and extracted with chloroform. The chloroform layer was washed with aqueous sodium hydroxide solution and water, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 11.0 g of crude 1-butyl-2,5-dichlorobenzimidazole. Then, the obtained crude 1-butyl-2,5-dichlorobenzimidazole (7.0 g) and piperazine

(10.0 g) were added to xylene (20 ml), and the mixture was refluxed for 3 hrs. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography [eluted with a mixed solvent of chloroform:methanol=4:1] to give 1.5 g of the title compound.

10 [0060] mp 102.0-105.0°C NMR (CDCl_3 , δ ppm): 0.67-
2.24(7H,m), 2.40(1H,s), 2.84-3.64(8H,m), 4.04(2H,t), 6.99-
7.84(3H,m). Elemental analysis for $\text{C}_{15}\text{H}_{21}\text{ClN}_4$: Calculated
(%)C, 61.53; H, 7.23; N, 19.13 Found (%)C, 61.33; H, 7.35; N, 18.95

15 [0061] Example 7 5-chloro-2-(4-methyl-1-piperazinyl)-1-tetrahydrofurfurylbenzimidazole: In the same manner as in Example 1 except that 5-chloro-1-tetrahydrofurfuryl-2-benzimidazolone (see Production Example 1, compound No. 5, Table 2) was used instead of 5-chloro-1-ethyl-2-benzimidazolone, the title compound was obtained, though 20 recrystallized from isopropyl alcohol.

25 [0062] mp 96.0-98.0°C NMR (CDCl_3 , δ ppm): 1.30-
2.23(4H,m), 2.38(3H,s), 2.46-2.90(4H,m), 3.20-3.60(4H,m), 3.60-4.60(5H,m), 7.00-7.82(3H,m). Elemental analysis for $\text{C}_{17}\text{H}_{23}\text{ClN}_4\text{O}$: Calculated (%)C, 60.98; H, 6.92; N, 16.73 Found (%)C, 60.87; H, 6.76; N, 16.80

30 [0063] Example 8 1-(2-butyl)-5-chloro-2-(4-methyl-1-piperazinyl)benzimidazole: 1-(2-Butyl)-5-chloro-2-benzimidazolone (see Production Example 1, compound No. 6, Table 2) (23 g) was refluxed in phosphorus oxychloride (23 ml) for 3 hrs. After allowing to cool, the reaction mixture was poured into ice water and extracted with chloroform. The chloroform layer was washed with aqueous sodium hydroxide solution and water, and dried over anhydrous magnesium sulfate. The solvent was evaporated

under reduced pressure to give 23.0 g of crude 1-(2-butyl)-2,5-dichlorobenzimidazole. Then, the obtained crude 1-(2-butyl)-2,5-dichlorobenzimidazole (17.0 g) and N-methylpiperazine (28.0 g) were mixed and stirred at 5 140°C for 2.5 hrs. Aqueous sodium hydroxide solution was added to the reaction mixture and the mixture was extracted with chloroform. The chloroform layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced 10 pressure to give 16 g of the title compound. A part thereof was applied to silica gel chromatography [eluted with a mixed solvent of chloroform:methanol=10:1] and recrystallized from acetonitrile. The resulting crystals showed the following property values.

15 [0064] mp 104.0-106.0°C NMR (CDCl_3 , δ ppm): 0.69(3H,t), 1.61(3H,d), 1.78-2.11(2H,m), 2.49(3H,s), 2.51-2.96(4H,m), 3.09-3.66(4H,m), 3.96-4.76(1H,m), 7.04-7.87(3H,m). Elemental analysis for $\text{C}_{16}\text{H}_{23}\text{ClN}_4$: Calculated (%C, 62.63; H, 7.56; N, 18.26 Found (%C, 62.73; H, 7.70; N, 18.37

20 [0065] Example 9 5-chloro-1-isobutyl-2-(4-methyl-1-piperazinyl)benzimidazole: By reaction in the same manner as in Example 8 except that 5-chloro-1-isobutyl-2-benzimidazolone (see Production Example 1, compound No. 7, Table 2) was used instead of 1-(2-butyl)-5-chloro-2-benzimidazolone, followed by purification by silica gel 25 chromatography [eluted with a mixed solvent of chloroform:methanol=20:1], the title compound was obtained.

[0066] mp 145.0-147.0°C NMR (CDCl_3 , δ ppm): 0.87(6H,d), 1.78-2.41(1H,m), 2.42(3H,s), 2.53-2.98(4H,m), 3.08-3.70(4H,m), 3.86(2H,d), 6.98-7.98(3H,m). Elemental analysis for $\text{C}_{16}\text{H}_{23}\text{ClN}_4$: Calculated (%C, 62.63; H, 7.56; N, 18.26 Found (%C, 62.61; H, 7.70; N, 18.26

30 [0067] Example 10 5-chloro-2-(4-methyl-1-piperazinyl)-1-(3-pentyl)benzimidazole fumarate: In the same manner as

in Example 8 except that 5-chloro-1-(3-pentyl)-2-benzimidazolone (see Production Example 1, compound No. 8, Table 2) was used instead of 1-(2-butyl)-5-chloro-2-benzimidazolone, 5-chloro-2-(4-methyl-1-piperazinyl)-1-(3-pentyl)benzimidazole was obtained. Then, in the same manner as in Example 5, the compound was converted to fumarate, which was recrystallized from ethanol to give the title compound.

[0068] mp 201.0-202.0°C NMR (DMSO-d₆, δ ppm):

10 0.69(6H,t), 1.51-2.19(4H,m), 2.37(3H,s), 2.47-2.99(4H,m), 3.00-3.51(4H,m), 3.70-4.50(1H,m), 6.60(2H,s), 6.93-7.64(3H,m), 10.11(2H,brs).

Elemental analysis for C₁₇H₂₅ClN₄·C₄H₄O₄: Calculated (%): C, 57.73; H, 6.69; N, 12.82 Found (%): C, 57.54; H, 6.63; N, 12.76

15 [0069] Example 11 5-chloro-1-cyclopentyl-2-(4-methyl-1-piperazinyl)benzimidazole: By reaction in the same manner as in Example 8 except that 5-chloro-1-cyclopentyl-2-benzimidazolone (see Production Example 1, compound No. 9, Table 2) was used instead of 1-(2-butyl)-5-chloro-2-benzimidazolone, followed by recrystallization from acetonitrile, the title compound was obtained.

[0070] mp 168.0-171.0°C NMR (CDCl₃, δ ppm): 1.26-2.36(8H,m), 2.38(3H,s), 2.49-2.93(4H,m), 3.07-3.64(4H,m), 4.26-5.26(1H,m), 6.96-7.86(3H,m). Elemental analysis for C₁₇H₂₃ClN₄: Calculated (%): C, 64.04; H, 7.27; N, 17.57 Found (%): C, 64.00; H, 7.17; N, 17.75

25 [0071] Example 12 5-chloro-1-(3-ethoxypropyl)-2-(4-methyl-1-piperazinyl)benzimidazole: By reaction in the same manner as in Example 8 except that 5-chloro-1-(3-ethoxypropyl)-2-benzimidazolone (see Production Example 1, compound No. 10, Table 2) was used instead of 1-(2-butyl)-5-chloro-2-benzimidazolone, followed by recrystallization from hexane, the title compound was obtained.

[0072] mp 72.0-74.0°C NMR (CDCl₃, δ ppm): 1.21(3H,t), 1.72-

2.24(2H,m), 2.38(3H,s), 2.49-2.82(4H,m), 3.20-
3.79(8H,m), 4.15(2H,t), 7.04-7.82(3H,m). Elemental analysis
for C₁₇H₂₅ClN₄O · 1/4 H₂O Calculated
(%)C, 59.81; H, 7.53; N, 16.41 Found (%)C, 59.84; H, 7.50; N, 16.47

5 [0073] Example 13 1-ethyl-5-methyl-2-(4-methyl-1-
piperazinyl)benzimidazole · 2fumarate: In the same manner
as in Example 8 except that 1-ethyl-5-methyl-2-
benzimidazolone [Helv. Chim. Acta, 59(1), 148-155 (1976)]
was used instead of 1-(2-butyl)-5-chloro-2-benzimidazolone,
10 1-ethyl-5-methyl-2-(4-methyl-1-piperazinyl)benzimidazole
was obtained. Then, in the same manner as in Example 5,
the compound was converted to fumarate, which was
recrystallized from acetonitrile to give the title
compound.

15 [0074] mp 168.0-171.0°C NMR (CDCl₃, δ ppm):
1.34(3H,t), 2.48(3H,s), 2.57(3H,s), 2.75-3.18(4H,m), 3.18-3.60
(4H,m), 4.07(2H,q), 6.64(4H,s), 6.82-7.50(3H,m), 11.04(4H,brs).
Elemental analysis for C₁₅H₂₂N₄ · 2C₄H₄O₄ Calculated
(%)C, 56.32; H, 6.16; N, 11.42 Found (%)C, 56.28; H, 6.03; N, 11.56

20 [0075] Example 14 1-butyl-5-methyl-2-(4-methyl-1-
piperazinyl)benzimidazole · 3/2 fumarate: In the same
manner as in Example 8 except that 1-butyl-5-methyl-2-
benzimidazolone (see Production Example 1, compound No. 11,
Table 2) was used instead of 1-(2-butyl)-5-chloro-2-
25 benzimidazolone, 1-butyl-5-methyl-2-(4-methyl-1-
piperazinyl)benzimidazole was obtained. Then, in the same
manner as in Example 5, the compound was converted to
fumarate, which was recrystallized from ethanol to give
the title compound.

30 [0076] mp 147.0-162.0°C NMR (DMSO-d₆, δ ppm): 0.52-
2.10(7H,m), 2.47(3H,s), 2.52(3H,s), 2.70-3.12(4H,m), 3.12-3.67
(4H,m), 4.01(2H,t), 6.62(3H,s), 6.82-7.52(3H,m), 8.69(3H,brs).
Elemental analysis for C₁₇H₂₆N₄ · 3/2C₄H₄O₄ Calculated
(%)C, 59.99; H, 7.00; N, 12.17 Found (%)C, 59.83; H, 6.80; N, 12.11

[0077] Example 15 1-isobutyl-5-methyl-2-(4-methyl-1-piperazinyl)benzimidazole: By reaction in the same manner as in Example 8 except that 1-isobutyl-5-methyl-2-benzimidazolone (see Production Example 1, compound No. 12, Table 2) was used instead of 1-(2-butyl)-5-chloro-2-benzimidazolone, followed by silica gel chromatography [eluted with a mixed solvent of chloroform:methanol=10:1], then recrystallization from hexane, the title compound was obtained.

[0078] mp 119.0-121.0°C NMR (CDCl_3 , δ ppm):
0.85(6H,d), 1.90-2.38(1H,m), 2.38(3H,s), 2.44(3H,s), 2.50-2.90(4H,m), 3.10-3.60 (4H,m), 3.80(2H,d), 6.80-7.60(3H,m).

Elemental analysis for $\text{C}_{17}\text{H}_{26}\text{N}_4$ Calculated (%): C, 71.29; H, 9.15; N, 19.56 Found (%): C, 71.29; H, 9.28; N, 19.73

[0079] Example 16 5-methyl-1-(3-ethoxypropyl)-2-(4-methyl-1-piperazinyl)benzimidazole fumarate: By reaction in the same manner as in Example 8 except that 1-(3-ethoxypropyl)-5-methyl-2-benzimidazolone (see Production Example 1, compound No. 13, Table 2) was used instead of 1-(2-butyl)-5-chloro-2-benzimidazolone, followed by silica gel chromatography [eluted with a mixed solvent of chloroform:methanol=8:1], 5-methyl-1-(3-ethoxypropyl)-2-(4-methyl-1-piperazinyl)benzimidazole was obtained. Then, in the same manner as in Example 5, the compound was converted to fumarate, which was recrystallized from ethanol to give the title compound.

[0080] mp 149.0-150.0°C NMR (DMSO-d_6 , δ ppm):
1.13(3H,t), 1.50-2.20(2H,m), 2.35(3H,s), 2.45-2.98(4H,m), 3.00-3.70(8H,m), 4.07(2H,t), 6.61(2H,s), 6.76-7.42(3H,m), 9.36(2H,brs). Elemental analysis for $\text{C}_{18}\text{H}_{28}\text{N}_4\text{O} \cdot \text{C}_4\text{H}_4\text{O}_4 \cdot 3/4\text{H}_2\text{O}$ Calculated (%): C, 59.24; H, 7.57; N, 12.56 Found (%): C, 59.37; H, 7.61; N, 12.66

[0081] Example 17 1-butyl-5-fluoro-2-(4-methyl-1-piperazinyl)benzimidazole 3/2 fumarate: By reaction in

the same manner as in Example 8 except that 1-butyl-5-fluoro-2-benzimidazolone (see Production Example 1, compound No. 14, Table 2) was used instead of 1-(2-butyl)-5-chloro-2-benzimidazolone, followed by silica gel chromatography [eluted with a mixed solvent of chloroform:methanol=13:1], 1-butyl-5-fluoro-2-(4-methyl-1-piperazinyl)benzimidazole was obtained. Then, in the same manner as in Example 5, the compound was converted to fumarate, which was recrystallized from ethanol to give the title compound.

[0082] mp 170.0-172.0°C NMR (DMSO-d₆, δ ppm): 0.68-2.20(7H,m), 2.52(3H,s), 2.70-3.14(4H,m), 3.14-3.70(4H,m), 4.08(2H,t), 6.63(3H,s), 6.72-7.70(3H,m), 10.12(3H,brs). Elemental analysis for C₁₆H₂₃FN₄ · 3/2C₄H₄O₄ Calculated (%)C, 56.89; H, 6.29; N, 12.06 Found (%)C, 56.95; H, 6.17; N, 12.13

[0083] Example 18 5-chloro-1-(2-ethoxyethyl)-2-(4-methyl-1-piperazinyl)benzimidazole · 2maleate: By reaction in the same manner as in Example 8 except that 5-chloro-1-(2-ethoxyethyl)-2-benzimidazolone (see Production Example 1, compound No. 15, Table 2) was used instead of 1-(2-butyl)-5-chloro-2-benzimidazolone, followed by silica gel chromatography [eluted with a mixed solvent of chloroform:methanol=10:1], 5-chloro-1-(2-ethoxyethyl)-2-(4-methyl-1-piperazinyl)benzimidazole was obtained. Then, in the same manner as in Example 5 except that maleic acid was used instead of fumaric acid, the compound was converted to maleate, which was recrystallized from a mixed solvent of ethyl acetate-ethanol to give the title compound.

[0083] mp 127.0-129.0°C NMR (DMSO-d₆, δ ppm): 1.00(3H,t), 2.89(3H,s), 3.04-3.95(12H,m), 4.24(2H,t), 6.15(4H,s), 6.91-7.62(3H,m), 11.40(4H,brs). Elemental analysis for C₁₆H₂₃N₄OCl · 2C₄H₄O₄ Calculated (%)C, 51.94; H, 5.63; N, 10.10 Found

(%)C, 51.90; H, 5.79; N, 10.23

[0084] Example 19 1-cyclopentyl-5-methyl-2-(4-methyl-1-piperazinyl)benzimidazole: By reaction in the same manner as in Example 8 except that 1-cyclopentyl-5-methyl-2-benzimidazolone (see Production Example 1, compound No. 16, Table 2) was used instead of 1-(2-butyl)-5-chloro-2-benzimidazolone, followed by recrystallization from ethyl acetate, the title compound was obtained.

[0085] mp 125.0-125.5°C NMR (CDCl_3 , δ ppm): 1.30-10 2.30(8H,m), 2.36(3H,s), 2.43(3H,s), 2.49-2.95(4H,m), 3.07-3.62(4H,m), 4.27-5.17(1H,m), 6.77-7.67(3H,m). Elemental analysis for $\text{C}_{18}\text{H}_{26}\text{N}_4 \cdot 1/10 \text{H}_2\text{O}$ Calculated

(%)C, 72.01; H, 8.80; N, 18.66 Found (%)C, 71.91; H, 8.79; N, 18.67

[0086] Example 20 6-amino-5-chloro-1-ethyl-2-(4-methyl-1-piperazinyl)benzimidazole: 5-Chloro-1-ethyl-2-(4-methyl-1-piperazinyl)benzimidazole (see Example 1)(2.5 g) was dissolved in acetic acid (4 ml). Fuming nitric acid (3.8 g) was added and the mixture was stirred at 60°C for 40 min. The reaction mixture was poured into ice water, neutralized with 2N sodium hydroxide solution and extracted with chloroform. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 2.8 g of 5-chloro-1-ethyl-2-(4-methyl-1-piperazinyl)-6-nitrobenzimidazole. Then, the obtained 5-chloro-1-ethyl-(4-methyl-1-piperazinyl)-6-nitrobenzimidazole (2.0 g) was suspended in a mixed solvent of ethanol (15 ml) and concentrated hydrochloric acid (4 ml). Zinc powder (2.4 g) was added by small portions and the mixture was stirred at 60°C for 30 min. Aqueous ammonia was added to alkalinify the solution and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was

applied to silica gel chromatography [eluted with a mixed solvent of chloroform:methanol=10:1] and recrystallized from acetonitrile to give 0.5 g of the title compound.

[0087] mp 184.0-187.0°C NMR (CDCl_3 , δ ppm):

5 1.37(3H,t), 2.35(3H,s), 2.45-2.90(4H,m), 3.02-
3.60(4H,m), 3.70-4.40(4H,m), 6.63(1H,s), 7.52(1H,s).

Elemental analysis for $\text{C}_{14}\text{H}_{20}\text{ClN}_5$: Calculated

(%)C, 57.23; H, 6.86; N, 23.84 Found (%)C, 57.36; H, 6.73; N, 23.82

In the following, the compounds of Examples 21-36 were

10 obtained in the same manner as in Example 20 except that the corresponding compounds [the compound of the formula (I) wherein R₄ is hydrogen atom] described in the aforementioned Examples were used instead of 5-chloro-1-ethyl-2-(4-methyl-1-piperazinyl)benzimidazole in Example

15 20. In Example 35, fumarate was further derived in the same manner as in Example 5.

[0088] Example 21 6-amino-5-chloro-1-cyclopropyl-2-(4-methyl-1-piperazinyl)benzimidazole: mp 205.0

(decomposition)

20 NMR (CDCl_3 , δ ppm): 0.94-1.47(4H,m), 2.39(3H,s), 2.47-
2.83(4H,m), 2.83-3.27(1H,m), 3.27-
3.73(4H,m), 3.98(2H,brs), 6.80(1H,s), 7.60(1H,s). Elemental
analysis for $\text{C}_{15}\text{H}_{20}\text{ClN}_5$: Calculated

(%)C, 58.91; H, 6.59; N, 22.90 Found (%)C, 58.83; H, 6.49; N, 23.01

25 [0089] Example 22 6-amino-5-chloro-2-(4-methyl-1-piperazinyl)-1-propylbenzimidazole: mp 180.5-182.0°C NMR
(CDCl_3 , δ ppm): 0.90(3H,t), 1.40-
2.20(2H,m), 2.35(3H,s), 2.45-2.87(4H,m), 3.05-
3.60(4H,m), 3.62-4.30(4H,m), 6.57(1H,s), 7.47(1H,s).

30 Elemental analysis for $\text{C}_{15}\text{H}_{22}\text{ClN}_5$: Calculated

(%)C, 58.53; H, 7.20; N, 22.75 Found (%)C, 58.45; H, 7.07; N, 22.73

[0090] Example 23 6-amino-5-chloro-1-methyl-2-(4-methyl-1-piperazinyl)benzimidazole: mp 181.0-183.0°C NMR (CDCl_3 , δ ppm): 2.34(3H,s), 2.44-2.81(4H,m), 3.07-

3.40(4H,m), 3.44(3H,s), 3.95(2H,brs), 6.51(1H,s), 7.43(1H,s).

Elemental analysis for C₁₃H₁₈ClN₅: Calculated

(%)C, 55.81; H, 6.48; N, 25.03 Found (%)C, 55.83; H, 6.40; N, 24.97

5 [0091] Example 24 6-amino-1-butyl-5-chloro-2-(4-methyl-1-piperazinyl)benzimidazole: mp 160.0-164.0°C NMR (CDCl₃, δ ppm): 0.66-2.16(7H,m), 2.37(3H,s), 2.46-2.80(4H,m), 3.14-3.55(4H,m), 3.61-4.56(4H,m), 6.65(1H,s), 7.54(1H,s).

Elemental analysis for C₁₆H₂₄ClN₅: Calculated

(%)C, 59.71; H, 7.52; N, 21.76 Found (%)C, 59.62; H, 7.41; N, 21.73

10 [0092] Example 25 6-amino-5-chloro-2-(4-methyl-1-piperazinyl)-1-(2-butyl)benzimidazole: mp 207.0-210.0°C NMR (CDCl₃, δ ppm): 0.70(3H,t), 1.57(3H,d), 1.77-2.32(2H,m), 2.40(3H,s), 2.50-2.97(4H,m), 2.97-3.62(4H,m), 3.82-4.80(3H,m), 6.90(1H,s), 7.65(1H,s).

15 Elemental analysis for C₁₆H₂₄ClN₅: Calculated

(%)C, 59.71; H, 7.52; N, 21.76 Found (%)C, 59.73; H, 7.70; N, 21.75

20 [0093] Example 26 6-amino-5-chloro-1-isobutyl-2-(4-methyl-1-piperazinyl)benzimidazole: mp 157.0-159.0°C NMR (CDCl₃, δ ppm): 0.84(6H,d), 1.62-2.33(1H,m), 2.38(3H,s), 2.48-2.92(4H,m), 3.02-3.60(4H,m), 3.60-4.52(4H,m), 6.67(1H,s), 7.60(1H,s).

Elemental analysis for C₁₆H₂₄ClN₅: Calculated

(%)C, 59.71; H, 7.52; N, 21.76 Found (%)C, 59.78; H, 7.69; N, 21.69

25 [0094] Example 27 6-amino-5-chloro-(4-methyl-1-piperazinyl)-1-(3-pentyl)benzimidazole: mp 220.0-221.0°C NMR (CDCl₃, δ ppm): 0.76(6H,t), 1.50-2.29(4H,m), 2.35(3H,s), 2.47-2.90(4H,m), 3.00-3.45(4H,m), 3.60-4.50(3H,m), 6.74(1H,s), 7.51(1H,s).

Elemental analysis for C₁₇H₂₆ClN₅: Calculated

30 (%)C, 60.79; H, 7.80; N, 20.85 Found (%)C, 60.86; H, 7.95; N, 20.99

[0095] Example 28 6-amino-5-chloro-1-cyclopentyl-2-(4-methyl-1-piperazinyl)benzimidazole: mp 220.5-222.5°C NMR (CDCl₃, δ ppm): 1.43-2.30(8H,m), 2.36(3H,s), 2.46-2.93(4H,m), 3.10-3.55(4H,m), 3.87(2H,brs), 4.30-

5.13(1H,m), 6.65(1H,s), 7.49(1H,s). Elemental analysis for C₁₇H₂₄ClN₅: Calculated (%C, 61.16; H, 7.25; N, 20.98 Found (%C, 61.06; H, 7.08; N, 21.15

5 [0096] Example 29 6-amino-5-chloro-1-(3-ethoxypropyl)-2-(4-methyl-1-piperazinyl)benzimidazole: mp 119.0-120.0°C

NMR (CDCl₃, δ ppm): 1.26(3H,t), 1.74-2.34(2H,m), 2.42(3H,s), 2.51-2.95(4H,m), 3.10-3.82(8H,m), 3.82-4.44(4H,m), 6.85(1H,s), 7.71(1H,s).

10 Elemental analysis for C₁₇H₂₆ClN₅O: Calculated (%C, 58.03; H, 7.45; N, 19.90 Found (%C, 57.92; H, 7.56; N, 19.81

15 [0097] Example 30 6-amino-5-chloro-2-(4-methyl-1-piperazinyl)-1-tetrahydrofurfurylbenzimidazole: mp 163.0-165.0°C NMR (CDCl₃, δ ppm): 1.50-2.19(4H,m), 2.33(3H,s), 2.42-2.80(4H,m), 3.07-3.40(4H,m), 3.50-4.50(7H,m), 6.75(1H,s), 7.49(1H,s).

20 Elemental analysis for C₁₇H₂₄ClN₅O: Calculated (%C, 58.36; H, 6.91; N, 20.02 Found (%C, 58.20; H, 6.88; N, 20.06

25 [0098] Example 31 6-amino-1-ethyl-5-methyl-2-(4-methyl-1-piperazinyl)benzimidazole: mp 148.0-153.0°C

30 (recrystallized from ethanol) NMR (CDCl₃, δ ppm): 1.36(3H,t), 2.22(3H,s), 2.33(3H,s), 2.46-3.00(4H,m), 3.10-3.45(4H,m), 3.60(2H,brs), 3.96(2H,q), 6.60(1H,s), 7.37(1H,s).

Elemental analysis for C₁₅H₂₃N₅·1/4 H₂O: Calculated (%C, 64.83; H, 8.52; N, 25.20 Found (%C, 64.91; H, 8.63; N, 25.24

35 [0099] Example 32 6-amino-1-butyl-5-methyl-2-(4-methyl-1-piperazinyl)benzimidazole: mp 155.0-158.0°C NMR (CDCl₃, δ ppm): 0.60-2.10(7H,m), 2.25(3H,s), 2.37(3H,s), 2.48-3.07(4H,m), 3.07-3.45(4H,m), 3.60(2H,brs), 3.90(2H,t), 6.52(1H,s), 7.33(1H,s).

40 Elemental analysis for C₁₇H₂₇N₅: Calculated (%C, 67.74; H, 9.03; N, 23.23 Found (%C, 67.88; H, 9.21; N, 23.18

45 [0100] Example 33 6-amino-1-isobutyl-5-methyl-2-(4-methyl-1-piperazinyl)benzimidazole: mp 122.0-124.0°C (recrystallized from isopropyl alcohol) NMR (CDCl₃, δ

ppm): 0.83(6H,d), 1.47-
2.17(1H,m), 2.22(3H,s), 2.34(3H,s), 2.43-2.87(4H,m), 2.97-
3.38(4H,m), 3.47(2H,brs), 3.71(2H,d), 6.53(1H,s), 7.32(1H,s).

Elemental analysis for C₁₇H₂₇N₅: Calculated

5 (%)C, 67.74; H, 9.03; N, 23.23 Found (%)C, 67.62; H, 9.22; N, 23.02

[0101] Example 34 6-amino-1-cyclopentyl-5-methyl-2-(4-methyl-1-piperazinyl)benzimidazole: mp 194.0-196.0°C
(recrystallized from a mixed solvent of dioxane-hexane)

NMR (CDCl₃, δ ppm): 1.38-

10 2.20(8H,m), 2.24(3H,s), 2.36(3H,s), 2.48-2.98(4H,m), 2.98-
3.38(4H,m), 3.50(2H,brs), 4.23-
5.18(1H,m), 6.66(1H,s), 7.27(1H,s). Elemental analysis for
C₁₈H₂₇N₅: Calculated (%)C, 68.97; H, 8.68; N, 22.34 Found
(%)C, 68.90; H, 8.76; N, 22.46

15 [0102] Example 35 6-amino-1-(3-ethoxypropyl)-5-methyl-2-(4-methyl-1-piperazinyl)benzimidazole · ifumarate: mp
198.0-199.0°C (decomposition) (recrystallized from
ethanol)

NMR (DMSO-d₆, δ ppm): 1.12(3H,t), 1.46-

20 1.98(2H,m), 2.11(3H,s), 2.40(3H,s), 2.56-2.96(4H,m), 2.96-
3.66(8H,m), 3.91(2H,t), 6.53(3H,s), 6.69-7.30(5H,m).

Elemental analysis for C₁₈H₂₉N₅O·C₄H₄O₄·1/2 H₂O: Calculated
(%)C, 57.88; H, 7.51; N, 15.34 Found (%)C, 57.87; H, 7.30; N, 15.36

[0103] Example 36 6-amino-1-butyl-5-fluoro-2-(4-methyl-1-piperazinyl)benzimidazole: mp 124.5-125.0°C NMR (CDCl₃, δ
ppm): 0.47-2.17(7H,m), 2.35(3H,s), 2.44-2.85(4H,m), 2.85-
3.57(4H,m), 3.57-4.57(4H,m), 6.60(1H,d), 7.15(1H,d).

Elemental analysis for C₁₆H₂₄N₅F: Calculated

(%)C, 62.93; H, 7.92; N, 22.93 Found (%)C, 62.86; H, 7.71; N, 22.86

30 [0104] Example 37 6-amino-2-(4-amino-1-piperazinyl)-5-chloro-1-isopropylbenzimidazole: (1) 5-Chloro-1-isopropyl-
6-nitro-2-(1-piperazinyl)benzimidazole (see Production
Example 2) (0.32 g) was suspended in 4N hydrochloric acid
(3 ml) and sodium nitrite (0.07 g) was added. The mixture

was stirred at 60°C for 1 hr. The reaction mixture was washed with ethyl acetate, and the aqueous layer was alkalified with aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic layer was 5 washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was applied to silica gel chromatography [eluted with a mixed solvent of chloroform:methanol=10:1] to give 0.03 g of 5-chloro-1-
10 isopropyl-6-nitro-2-(4-nitroso-1-piperazinyl)benzimidazole. This was partially taken and recrystallized from dimethylformamide. The resulting crystals showed the following property values.

[0105] mp 216.0-218.0°C NMR (DMSO-d₆, δ ppm):

15 1.61(6H,d), 3.04-3.78(4H,m), 3.78-4.24(2H,m), 4.24-
5.14(3H,m), 7.68(1H,s), 8.30(1H,s). Elemental analysis for
C₁₄H₁₇ClN₆O₃: Calculated (%)C, 47.67; H, 4.86; N, 23.82 Found
(%)C, 47.53; H, 4.93; N, 24.02

[0106] (2) 5-Chloro-1-isopropyl-6-nitro-2-(4-nitroso-1-piperazinyl)benzimidazole (2.6 g) was added to ethanol (24 ml) and concentrated hydrochloric acid (6 ml) was added thereto. Then, zinc powder (3.0 g) was added and the mixture was stirred at 60°C for 6 min. Aqueous sodium hydroxide solution was added to alkalify the solution and 25 the mixture was extracted with chloroform. The chloroform layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was applied to silica gel chromatography [eluted with a mixed solvent of chloroform:methanol=50:1] to give 0.8 g of 6-amino-5-chloro-1-isopropyl-2-(4-nitroso-1-piperazinyl)benzimidazole. This was partially taken and recrystallized from ethyl acetate. The resulting crystals showed the following property values.

[0107] mp 172.0-174.0°C NMR (CDCl_3 , δ ppm):

1.82(6H,d), 2.72-5.32(11H,m), 7.09(1H,s), 7.76(1H,s).

Elemental analysis for $\text{C}_{14}\text{H}_{19}\text{ClN}_6\text{O}$: Calculated

(%)C, 52.09; H, 5.93; N, 26.04 Found (%)C, 52.24; H, 5.89; N, 25.91

5 [0108] (3) 6-Amino-5-chloro-1-isopropyl-2-(4-nitroso-1-piperazinyl)benzimidazole (0.4 g) was dissolved in acetic acid (10 ml) and zinc powder (0.5 g) was added. The mixture was stirred at 60°C for 10 min. Aqueous sodium hydroxide solution was added and the mixture was extracted 10 with chloroform. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was applied to silica gel chromatography [eluted with a mixed solvent of chloroform:methanol=10:1] to give 0.17 g of 6- 15 amino-2-(4-amino-1-piperazinyl)-5-chloro-1-isopropylbenzimidazole.

[0109] mp 175.0-179.0°C NMR (CDCl_3 , δ ppm):

1.53(6H,d), 2.60-3.11(4H,m), 3.11-4.70(8H,m), 4.70-

5.00(1H,m), 6.81(1H,s), 7.49(1H,s). Elemental analysis for

20 $\text{C}_{14}\text{H}_{21}\text{ClN}_6$: Calculated (%)C, 54.45; H, 6.85; N, 27.21. Found

(%)C, 54.66; H, 6.77; N, 27.07

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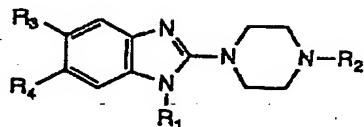
大阪府大東市川中新町16番409号

(54)【発明の名称】 ベンズイミダゾール誘導体

(57)【要約】

【構成】 一般式(I)

【化I】



(I)

[式中、R₁は低級アルキル基、低級アルコキシ(低級アルキル)基またはテトラヒドロフルフリル基を示し、R₂は水素原子、メチル基またはアミノ基を示し、R₃はハロゲン原子またはメチル基を示し、R₄は水素原子またはアミノ基を示す。]で表わされるベンズイミダゾール誘導体またはその薬理学的に許容される酸付加塩。

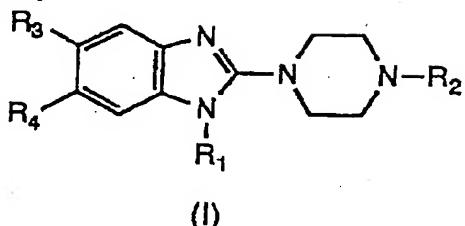
【効果】 上記の新規ベンズイミダゾール誘導体は、強力な5-HT₁拮抗作用を有し、制吐剤として有用である。

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【特許請求の範囲】

【請求項1】 一般式(I)

【化1】



[式中、R₁は低級アルキル基、低級アルコキシ（低級アルキル）基またはテトラヒドロフルフリル基を示し、R₂は水素原子、メチル基またはアミノ基を示し、R₃はハロゲン原子またはメチル基を示し、R₄は水素原子またはアミノ基を示す。]で表わされるベンズイミダゾール誘導体またはその薬理学的に許容される酸付加塩。

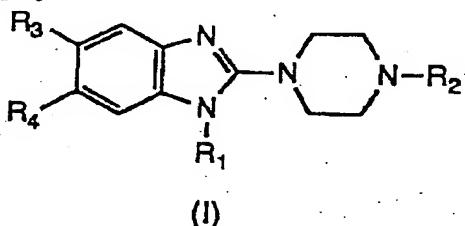
【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は新規なベンズイミダゾール誘導体に関する。さらに詳しくは、一般式(I)

【0002】

【化2】



[式中、R₁は低級アルキル基、低級アルコキシ（低級アルキル）基またはテトラヒドロフルフリル基を示し、R₂は水素原子、メチル基またはアミノ基を示し、R₃はハロゲン原子またはメチル基を示し、R₄は水素原子またはアミノ基を示す。]で表わされるベンズイミダゾール誘導体またはその薬理学的に許容される酸付加塩に関する。

【0003】本発明のベンズイミダゾール誘導体は強力なセロトニン拮抗作用を有し、制吐剤として有用である。

【0004】

【従来の技術】癌治療においてシスプラチン等の化学療法剤の存在は欠くことのできないものである。しかし、その一方で嘔吐等の副作用が問題となり、治療の継続を困難にしている。

【0005】最近、この嘔吐の発現は、セロトニン[5-ヒドロキシトリプタミン（以下、5-HTと言ふ）]受容体の1つと関連することが判ってきた。5-HTは体内の神経伝達物質の1つであり、5-HTが関与する受容体

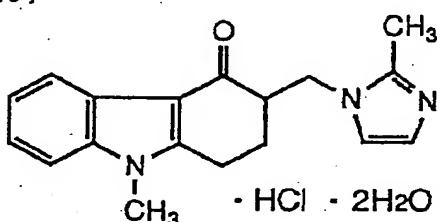
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は大別すると5-HT₁、5-HT₂、5-HT₃の3つが知られている。このうち癌化学療法に伴う嘔吐には5-HT₃受容体が関与している。つまり化学療法剤投与により5-HTが遊離し、その遊離した5-HTが腹部の5-HT₃受容体に結合することにより、腹部迷走神経を介して延髓第4脳室に存在する化学受容器引金帯そして嘔吐中枢が刺激され、その結果嘔吐が生じる。

【0006】5-HT₃拮抗作用を有するオンドンセトロン(GR38032F、下式参照)がシスプラチン等の化学療法剤の投与に伴う嘔吐の抑制に効果があることが報告されている[Cancer Chemother Pharmacol., 23, 389-391(1989)]。

【0007】

【化3】



20

【0008】一方、2-ビペラジニルベンズイミダゾール誘導体の医薬への応用については既に知られている。例えば、特開昭50-126682号には鎮痛、消炎作用を有する2-ビペラジニルベンズイミダゾール誘導体が開示されており、1-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール(化合物A)、2-(4-メチル-1-ビペラジニル)ベンズイミダゾール(化合物B)等が例示されている。また、特開昭58-79983号には抗ヒスタミン作用を有するベンズイミダゾール誘導体として1-(2-エトキシエチル)-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール・3/2フマル酸塩(化合物C)等のベンズイミダゾールの1位に低級アルコキシ(低級アルキル)基を有する化合物等が例示されている。しかし、これら2-ビペラジニルベンズイミダゾール誘導体の5-HT₃拮抗作用およびこれに基づく制吐作用については何ら知られていない。

【0009】

【0010】【発明が解決しようとする課題】本発明者等は5-HT₃拮抗作用を有し、シスプラチン等による癌化学療法に伴う嘔吐の抑制に有効な薬剤の開発を目指し、種々検討を加えた。

【0011】【発明の目的】本発明の目的は、斯かる要請を満足する新規な化合物を提供することにある。

【0012】

【課題を解決するための手段】本発明者等は検討を重ねた結果、前記一般式(I)で表わされる新規なベンズイミダゾール誘導体またはその薬理学的に許容される酸付加塩が、斯かる要請を満足することを見い出して本発明

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を完成した。

【0012】前記一般式(I)において、R₁で定義される基のうち、低級アルキル基は、炭素原子数1～5のアルキル基を表わし、該アルキル基は直鎖状でも分岐状でも環状でもよい。低級アルキル基の具体例としては、メチル基、エチル基、プロピル基、イソプロピル基、シクロプロピル基、ブチル基、2-ブチル基、イソブチル基、3-ベンチル基、シクロベンチル基等が挙げられる。また、低級アルコキシ(低級アルキル)基は、炭素原子数1～5のアルコキシ基で置換された炭素原子数1～5のアルキル基を表わす。低級アルコキシ(低級アルキル)基の具体例としては、2-エトキシエチル基、3*

*-エトキシプロピル基等が挙げられる。

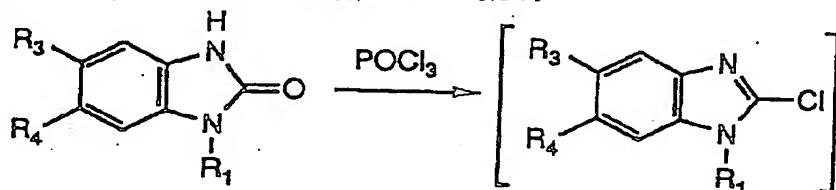
【0013】R₂で定義される基のうち、ハロゲン原子としてはクロル原子、フッ素原子等が挙げられる。

【0014】前記一般式(I)で表わされる本発明の化合物は例えば以下の何れかの方法によって製造することができる。

【0015】(A法)一般式(I)の化合物のうちR₂および/またはR₃がアミノ基でない化合物(R₂およびR₃は前記で定義される基に同じ)は、以下の方法によって製造することができる。

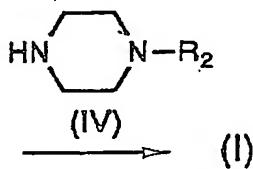
【0016】

【化4】



(II)

(III)



(IV)

(I)

(式中、R₁、R₂、R₃およびR₄は前記に同じ。ただし、R₂および/またはR₃がアミノ基の場合を除く。)

即ち、無溶媒もしくはクロロホルム等の不活性溶媒中、一般式(II)で表わされる化合物と、一般式(III)で表わされる化合物に対して通常2～6当量のオキシ塩化リントを60℃～溶媒の沸点温度で0.5～4時間反応させることにより化合物(IV)とする。次いで、これを精製することなく、無溶媒もしくはキシリレン等の不活性溶媒中、一般式(IV)で表わされる化合物と、一般式(IV)で表わされる化合物に対して通常2～6当量の一般式(IV)で表わされる化合物とを80～160℃または溶媒の沸点温度で1～4時間反応させることによって上記一般式(I)で表わされる化合物(式中、R₂および/またはR₃がアミノ基でない化合物)を製造することができる。

【0017】上記製造法において原料として用いられる一般式(II)で表わされる化合物は例えば、前記特開昭50-126682号に記載された方法に準じて製造することができる(後記製造例参照)。

【0018】(B法)一般式(I)の化合物のうちR₂がアミノ基で、R₃が水素原子である化合物(R₂およ

びR₃は前記で定義される基に同じ)は、上記A法により得られる一般式(I)の化合物で、R₂およびR₃がともに水素原子である化合物に、常法により、酸性水溶液中亜硝酸ナトリウムを作用させR₂がニトロソ基の化合物とし、次いで、亜鉛と酢酸等によりニトロソ基を還元することによって製造することができる。

【0019】(C法)一般式(I)の化合物のうちR₂が水素原子またはメチル基で、R₃がアミノ基である化合物(R₂およびR₃は前記で定義される基に同じ)は、上記A法により得られる一般式(I)の化合物でR₂が水素原子またはメチル基で、R₃が水素原子である化合物に、発煙硝酸を酢酸中で作用させるか、または濃硝酸を濃硫酸中-10～10℃で作用させて対応するR₂がニトロ基の化合物とし、次いで、無溶媒もしくはエタノール等の不活性溶媒中、通常4～7当量の還元剤を室温から溶媒の沸点温度で0.1～10時間作用させることによって製造することができる。

【0020】上記還元剤としては、例えば亜鉛と塩酸、鉄と塩酸、塩化第一スズと塩酸等が用いられる。

【0021】(D法)一般式(I)の化合物のうちR₂およびR₃がともにアミノ基である化合物(R₂およびR₃は前記で定義される基に同じ)は、一般式(I)の

化合物のうちR₁が水素原子で、R₂がニトロ基である化合物を上記C法と同様にして得、次いで、これを常法により酸性水溶液中亜硝酸ナトリウムを作用させR₂がニトロソ基の化合物とし、引き続き上記C法と同様にしてニトロ基を還元した後、上記B法と同様にして亜鉛と酢酸等によりニトロソ基を還元することによって製造することができる。

【0022】本発明の化合物(I)は、更に必要に応じ、常法に従って薬理学的に許容される酸付加塩に導くことができる。

【0023】本発明化合物の薬理学的に許容される酸付加塩としては、塩酸、硫酸等の無機酸との塩、マレイン酸、フマル酸等の有機酸との塩が挙げられる。

【0024】

【発明の作用効果】本発明化合物は、以下の試験例に示す通り5-HTにより誘発されたベゾルド・ヤーリッシュ反射(Bezold-Jarisch reflex)に対し、陽性対照化合物のオンダンセトロンに比して、強力な拮抗作用(5-HT₁拮抗作用)を示す。従って、本発明化合物は、その強力な5-HT₁拮抗作用に基づき、シスプラチン等の癌化学療法に伴う嘔吐の抑制剤として有用である。

【0025】以下、本発明化合物の作用効果を試験例を挙げて説明する。

【0026】試験例1

5-HT₁拮抗作用:

【0027】[試験化合物]

(1) 実施例1～18、20～37の化合物(本発明化合物)

(2) 1-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール・2マレイン酸塩(前記化合物Aの2マレイン酸塩)

(3) 2-(4-メチル-1-ビペラジニル)ベンズイ

ミダゾール(前記化合物B)

(4) 1-(2-エトキシエチル)-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール・3/2フマル酸塩(前記化合物C)

(5) オンダンセトロン(陽性対照化合物)

【0028】[試験方法] 5-HT₁拮抗作用は、5-HTによって誘発されるベゾルド・ヤーリッシュ反射(反射性徐脈)に対する拮抗作用を指標にして、Collins等の方法[Br.J.Pharmacol.,80,570P(1983)]に準じて測定した。

【0029】即ち、S.D.系雄性ラット(体重200～350g)をウレタン1.25mg/kgの腹腔内投与により麻酔し、頸動脈にカニューレを挿入し、心拍数を測定した。試験化合物を生理食塩液または5%エタノール生理食塩液に溶解し、静脈内投与(1μg/kg i.v.)した。試験化合物投与5分後、生理食塩液に溶解した5-HT₁を静脈内投与(0.04mg/kg i.v.)した。心拍数を測定し、試験化合物による反射性徐脈の抑制率を求め、5-HT₁拮抗作用を以下に示す評価基準に従って表わした。

【0030】抑制率: 20%未満; - , 20～50%; + , 50%以上; ++

なお、試験化合物のなかで陽性対照化合物のオンダンセトロンについては、1μg/kg i.v.において上記抑制効果が認め難かったので、3μg/kg i.v.における抑制率も併せて求めた。

【0031】[試験結果] 結果を第1表に示した。

【0032】第1表から明らかなように、本発明化合物は化合物A、BおよびCに比べ、また、オンダンセトロンに比べ強力な5-HT₁拮抗作用を有する。

【0033】

【表1】

第1表 5-HT ₃ 拮抗作用			
試験化合物 (実施例番号)	5-HT ₃ 拮抗作用 (1 μg/kg i.v.)	試験化合物 (実施例番号)	5-HT ₃ 拮抗作用 (1 μg/kg i.v.)
1	++	2 3	++
2	++	2 4	++
3	++	2 5	++
4	++	2 6	++
5	++	2 7	+
6	++	2 8	++
7	++	2 9	++
8	++	3 0	++
9	+	3 1	++
1 0	+	3 2	++
1 1	++	3 3	++
1 2	++	3 4	++
1 3	++	3 5	++
1 4	++	3 6	++
1 5	++	3 7	++
1 6	++	化合物A 化合物B 化合物C	- - -
1 7	++		
1 8	+		
2 0	++	オンダンセトロ ン	-(+*)
2 1	++		
2 2	++		

*: 3 μg/kg i.v.

【0034】

【実施例】以下に、製造例および実施例を挙げて、本発明を更に具体的に説明する。

【0035】製造例1

5-クロロ-1-エチル-2-ベンズイミダゾロン:

(1) 2,5-ジクロロニトロベンゼン25gをエチルアミン35gに加え封管中110°Cで3.5時間攪拌した。冷却後、反応混合物に水を加え酢酸エチルで抽出した。酢酸エチル層を水洗し、無水硫酸マグネシウムで乾燥した後、溶媒を濃縮して析出した結晶をろ取して4-クロロ-N-

エチル-2-ニトロアニリン(mp 90.5-93.0°C) 21gを得た。

【0036】(2) 4-クロロ-N-エチル-2-ニトロアニリン21gをエタノール100mlに溶解し、2.5N水酸化ナトリウム水溶液25mlを加えた。還流下、亜鉛末23gを少しづつ加え10分間攪拌した。不溶物をろ別し、水を加え酢酸エチルで抽出した。酢酸エチル層を水洗し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去して2-アミノ-4-クロロ-N-エチルアニリン(mp 62.0-64.0°C) 17gを得た。

【0037】(3) 2-アミノ-4-クロロ-N-エチルアニリン14gと尿素20gを160°Cで10時間攪拌した。冷却後、反応混合物に水を加え酢酸エチルで抽出した。酢酸エチル層を水洗し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去して5-クロロ-1-エチル-2-ベンズイミダゾロン15gを得た。なお、このものの一部をとってアセトニトリルから再結晶したものは以下の物性値を示した。

【0038】mp 170.0-172.0°C

NMR(CDCl₃, δ ppm): 1.27(3H, t), 3.84(2H, q), 6.65-7.15(3 H, m).

元素分析値(C₉H₁₁ClN₂Oとして) :

計算値(%) C, 54.97; H, 4.61; N, 14.25

実測値(%) C, 55.09; H, 4.58; N, 14.38

次に、製造例1の方法に従って、第2表に示す一般式(I I)の化合物(ただし、R₁は水素原子)を製造した。

【0039】

【表2】

第2表(その1)

No	R ₁	R ₃	mp (°C)	NMR(δ ppm) [溶媒]	元素分析値(%)		
					[分子式] 計算値(実測値) C H N		
1	メチル	C1	226.0 -228.0	[CDCl ₃]: 3.32(3H, s), 6.76- 7.36(3H, m), 10.86(1H, brs).	[C ₈ H ₇ ClN ₂ O] 52.62 3.86 15.34 (52.53 4.04 15.41)		
2	プロピル	C1	182.0 -184.0	[DMSO-d ₆]: 0.89(3H, t), 1. 22-2.15(2H, m), 3.74(2H, t), 6.55-7.35(3H, m), 10.97 (1H, brs).	[C ₁₀ H ₁₁ ClN ₂ O] 57.02 5.26 13.30 (56.86 5.25 13.39)		
3	シクロブ ロピル	C1	213.5 -214.5	[CDCl ₃]: 0.60-1.56(4H, m), 2.46-3.16(1H, m), 6.70-7. 39(3H, m) 10.54(1H, brs).	[C ₁₀ H ₉ ClN ₂ O] 57.57 4.35 13.43 (57.37 4.51 13.39)		
4	ブチル	C1	141.0 -143.0	[CDCl ₃]: 0.70-2.40(7H, m), 3.87(2H, t), 6.66-7.53(3H, m), 10.73(1H, brs).	[C ₁₁ H ₁₃ ClN ₂ O] 58.80 5.83 12.47 (59.00 5.81 12.32)		
5	テトラヒ ドロフル フェリル	C1	157.0 -158.5	[CDCl ₃]: 1.35-2.35(4H, m), 3.45-4.65(5H, m), 6.78-7. 39, (3H, m), 10.53(1H, brs).	[C ₁₂ H ₁₃ ClN ₂ O ₂] 57.04 5.19 11.09 (56.95 5.20 11.10)		
6	2-ブチ ル	C1	140.0 -142.0	[CDCl ₃]: 0.87(3H, t), 1.52 (3H, d), 1.67-2.47(2H, m), 4.04-4.82(1H, m), 6.77-7. 37, (3H, m), 11.04(1H, brs).	[C ₁₁ H ₁₃ ClN ₂ O] 58.80 5.83 12.47 (58.72 5.81 12.58)		

【0040】

【表3】

第2表(その2)

No	R ₁	R ₃	mp (°C)	NMR (δ ppm) [溶媒]	元素分析値 (%)		
					[分子式] 計算値(実測値)	C	H
7	イソブチル	C1	145.0 -153.0	[CDCl ₃]: 0.98(6H, d), 1.72- 2.72(1H, m), 3.65(2H, d), 6. 68-7.43(3H, m), 10.97(1H, brs).	[C ₁₁ H ₁₃ CIN ₂ O] 58.80 5.83 12.47 (58.81 5.74 12.47)		
8	3-ベンツル	C1	147.0 -148.0	[CDCl ₃]: 0.84(6H, t), 1.37- 2.45(4H, m), 3.87-4.57(1H, m), 6.80-7.37(3H, m), 11.19 (1H brs).	[C ₁₂ H ₁₅ CIN ₂ O] 60.38 6.33 11.74 (60.31 6.25 11.82)		
9	シクロヘキサメチル	C1	156.0 -158.0	[CDCl ₃]: 1.20-2.70(8H, m), 4.50-5.35(1H, m), 6.78-7.60 (3H, m), 10.95(1H, brs).	[C ₁₂ H ₁₃ CIN ₂ O] 60.89 5.54 11.83 (61.15 5.60 12.04)		
10	3-エトキシプロピル	C1	100.5 -102.0	[CDCl ₃]: 1.22(3H, t), 1.70- 2.45(2H, m), 3.15-3.75(4H, m), 3.99(2H, t), 6.75-7.45 (3H, m), 10.80(1H, brs).	[C ₁₂ H ₁₅ CIN ₂ O ₂] 56.59 5.94 11.00 (56.80 5.89 11.06)		
11	ブチル	CH ₃	128.0 -131.0	[DMSO-d ₆]: 0.31-1.91(7H, m), 2.28(3H, s), 3.68(2H, t), 6.41-7.10(3H, m), 10.63(1H, brs).	[C ₁₂ H ₁₆ N ₂ O] 70.56 7.89 13.71 (70.37 7.77 13.56)		
12	イソブチル	CH ₃	123.0 -125.0	[CDCl ₃]: 0.98(6H, d), 1.89- 2.82(1H, m), 2.37(3H, s), 3. 70(2H, d), 6.72-7.32(3H, m), 10.83(1H, brs).	[C ₁₂ H ₁₆ N ₂ O] 70.56 7.89 13.71 (70.41 8.07 13.80)		

[0041]

【表4】

第2表(その3)

No	R_1	R_3	mp (°C)	NMR (δ ppm) [溶媒]	元素分析値 (%)		
					[分子式] 計算値(実測値) C H N		
13	3-エキシプロピル	CH ₃	123.0 -125.5	[CDCl ₃]: 1.21(3H, t), 1.68-2.35(2H, m), 2.35(3H, s), 3.08-3.78(4H, m), 4.00(2H, t), 6.58-7.43(3H, m), 10.75(1H, brs).	[C ₁₃ H ₁₈ N ₂ O ₂] 66.64 7.74 11.96 (66.49 7.87 12.15)		
14	ブチル	F	111.0 -112.0	[CDCl ₃]: 0.57-2.17(7H, m), 3.86(2H, t), 6.52-7.22(3H, m), 10.75(1H, brs).	[C ₁₁ H ₁₃ FN ₂ O] 63.45 6.29 13.45 (63.54 6.43 13.42)		
15	2-エキシエチル	Cl	131.0 -133.0	[CDCl ₃]: 1.11(3H, t), 3.43(2H, q), 3.51-4.18(4H, m), 6.78-7.22(3H, m), 10.95(1H, brs)	[C ₁₁ H ₁₃ ClN ₂ O ₂] 54.98 5.44 11.64 (55.27 5.50 11.69)		
16	シクロヘン チル	CH ₃	147.0 -150.0	[CDCl ₃]: 1.17-2.67(8H, m), 2.34(3H, s), 4.42-5.27(1H, m), 6.62-7.24(3H, m), 10.72(1H, brs).	[C ₁₃ H ₁₆ N ₂ O ₂ ·1/2H ₂ O] 69.31 7.61 12.43 (69.27 7.52 12.41)		

【0042】製造例2

5-クロロ-1-イソプロピル-6-ニトロ-2-(1-ビペラジニル)ベンズイミダゾール:

(1) 2,5-ジクロロニドロベンゼン150gをイソプロピルアミン150gに加え封管中100°Cで4時間攪拌した。冷却後、反応混合物に水を加え酢酸エチルで抽出した。酢酸エチル層を水洗し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去して4-クロロ-N-イソプロピル-2-ニトロアニリン(mp 72.0-74.0°C) 163gを得た。

【0043】(2) 4-クロロ-N-イソプロピル-2-ニトロアニリン8gをエタノール20mlに溶解し、亜鉛末9.8gを加え、濃塩酸20mlを少しずつ加えた。混合物にアンモニア水を加えて中和し、酢酸エチルで抽出した。酢酸エチル層を水洗し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去した。残渣を蒸留(bp 90°C/0.4mmHg)することにより2-アミノ-4-クロロ-N

-イソプロピルアニリン(mp 35.0-36.0°C) 4.2gを得た。

【0044】(3) 2-アミノ-4-クロロ-N-イソプロピルアニリン14gと尿素15gを160°Cで3.5時間攪拌した。冷却後、反応混合物に水を加え酢酸エチルで抽出した。酢酸エチル層を希塗酸、水酸化ナトリウム水溶液、飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去した。残渣にイソプロピルアルコールを加え得られた結晶をろ取し、アセトニトリルから再結晶することにより5-クロロ-1-イソプロピル-2-ベンズイミダゾロン(mp 183.0-186.0°C) 7gを得た。

【0045】(4) 5-クロロ-1-イソプロピル-2-ベンズイミダゾロン4.0gをo-ジクロロベンゼン80mlに溶解し、70%硝酸2.0gを滴下した。60°Cで1時間攪拌した後放冷し、析出した結晶をろ取した。結晶をジエチルエーテルと水で洗浄し、5-クロロ-1-イソプロピ

ル-6-ニトロ-2-ベンズイミダゾロン (mp 270.0-272.0°C) 4.1gを得た。

[0046] (5) 5-クロロ-1-イソプロビル-6-ニトロ-2-ベンズイミダゾロン 1.0gに炭酸エチレン 0.7gとオキシ塩化リン 1.1ml を加え、5時間還流した。オキシ塩化リンを減圧下留去し、残渣を酢酸エチルに溶解して氷水中に加え、水酸化ナトリウム水溶液を加えて中和した。有機層を水洗し、無水硫酸マグネシウムで乾燥後、溶媒を減圧下に留去して 2,5-ジクロロ-1-イソプロビル-6-ニトロベンズイミダゾール (mp 150.5-152.5°C) 0.9gを得た。

[0047] (6) 2,5-ジクロロ-1-イソプロビル-6-ニトロベンズイミダゾール 4.6g とビペラジン 14.6g をトルエン中 50ml に加え、30分間還流した。反応混合物に水を加え、次いで、塩酸を加えて水層を酸性にした。水層を水酸化ナトリウム水溶液でアルカリ性にすることにより析出した結晶をろ取し、5-クロロ-1-イソプロビル-6-ニトロ-2-(1-ビペラジニル)ベンズイミダゾール 4.2gを得た。なお、このものの一部をとってエタノールから再結晶したものは以下の物性値を示した。

[0048] mp 179.0-180.0°C

NMR(CDCl₃, δ ppm): 1.65(6H, d), 1.82(1H, s), 2.95-3.65(8H, m), 4.37-5.10(1H, m), 7.77(1H, s), 8.17(1H, s).

元素分析値 (C₁₁H₁₂ClN₂O₂として) :

計算値 (%) C, 51.93; H, 5.60; N, 21.63

実測値 (%) C, 52.00; H, 5.68; N, 21.75

[0049] 実施例 1

5-クロロ-1-エチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール : 5-クロロ-1-エチル-2-ベンズイミダゾロン (製造例 1 参照) 2.1g をオキシ塩化リン 5ml 中で 1 時間還流した。放冷後、反応混合物を氷水に注ぎ、クロロホルムで抽出した。クロロホルム層を水酸化ナトリウム水溶液、水で洗浄し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去して粗製の 2,5-ジクロロ-1-エチルベンズイミダゾール 2.5gを得た。次いで、得られた粗製の 2,5-ジクロロ-1-エチルベンズイミダゾール 1.5g と N-メチルビペラジン 3.0g をキシレン 5ml 中に加え 2.5 時間還流した。反応混合物に水を加え酢酸エチルで抽出した。酢酸エチル層を水洗し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去した。残渣をシリカゲルクロマトグラフィー [クロロホルム: メタノール = 10:1 の混合溶媒で溶出] に付し、アセトニトリルから再結晶することにより標記化合物 0.9gを得た。

[0050] mp 124.0-125.5°C

NMR(CDCl₃, δ ppm): 1.40(3H, t), 2.35(3H, s), 2.40-2.73(4H, m), 3.11-3.50(4H, m), 3.99(2H, q), 7.0-7.6(3H, m),

元素分析値 (C₁₁H₁₄ClN₂O₂として) :

計算値 (%) C, 60.32; H, 6.87; N, 20.10

実測値 (%) C, 60.34; H, 6.87; N, 20.03

[0051] 実施例 2

5-クロロ-1-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール : 5-クロロ-1-エチル-2-ベンズイミダゾロン (製造例 1 第 2 表中の化合物 No.1 参照) を用いる他は実施例 1 と同様にして標記化合物を得た。

[0052] mp 139.0-141.0°C

10 NMR(CDCl₃, δ ppm): 2.39(3H, s), 2.52-2.96(4H, m), 3.17-3.56(4H, m), 3.59(3H, s), 6.87-7.87(3H, m).

元素分析値 (C₁₁H₁₄ClN₂O₂として) :

計算値 (%) C, 58.98; H, 6.47; N, 21.16

実測値 (%) C, 58.90; H, 6.38; N, 21.06

[0053] 実施例 3

5-クロロ-2-(4-メチル-1-ビペラジニル)-1-ブロビルベンズイミダゾール : 5-クロロ-1-エチル-2-ベンズイミダゾロンの替わりに 5-クロロ-1-ブロビル-2-ベンズイミダゾロン (製造例 1 第 2 表中の化合物 No.2 参照) を用いる他は実施例 1 と同様にして標記化合物を得た。(ただし、イソプロビルエーテルから再結晶した。)

[0054] mp 89.0-91.0°C

NMR(CDCl₃, δ ppm): 0.92(3H, t), 1.45-2.10(2H, m), 2.36(3H, s), 2.45-2.85(4H, m), 3.18-3.57(4H, m), 3.93(2H, t), 7.02-7.73(3H, m).

元素分析値 (C₁₁H₁₄ClN₂O₂として) :

計算値 (%) C, 61.53; H, 7.23; N, 19.13

実測値 (%) C, 61.37; H, 7.13; N, 19.26

30 [0055] 実施例 4

5-クロロ-1-シクロプロビル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール : 5-クロロ-1-エチル-2-ベンズイミダゾロンの替わりに 5-クロロ-1-シクロプロビル-2-ベンズイミダゾロン (製造例 1 第 2 表中の化合物 No.3 参照) を用いる他は実施例 1 と同様にして標記化合物を得た。(ただし、イソプロビルアルコールから再結晶した。)

[0056] mp 105.5-106.5°C

40 NMR(CDCl₃, δ ppm): 0.90-1.40(4H, m), 2.37(3H, s), 2.46-2.87(4H, m), 2.87-3.35(1H, m), 3.35-3.82(4H, m), 6.90-7.65(3H, m).

元素分析値 (C₁₁H₁₄ClN₂O₂として) :

計算値 (%) C, 61.96; H, 6.59; N, 19.27

実測値 (%) C, 62.02; H, 6.61; N, 19.18

[0057] 実施例 5

1-ブチル-5-クロロ-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール-3/2 フマル酸塩 : 1-ブチル-5-クロロ-2-ベンズイミダゾロン (製造例 1 第 2 表中の化合物 No.4 参照) 5.0g をオキシ塩化リン 7m

50 l 中で 2 時間還流した。放冷後、反応混合物を氷水に注

ぎ、クロロホルムで抽出した。クロロホルム層を水酸化ナトリウム水溶液、水で洗浄し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去して粗製の1-ブチル-2,5-ジクロロベンズイミダゾール4.5gを得た。次いで、得られた粗製の1-ブチル-2,5-ジクロロベンズイミダゾール3.0gとN-メチルビペラジン5.0gをキシレン20ml中に加え、3時間還流した。反応混合物に水を加え酢酸エチルで抽出した。酢酸エチル層を水洗し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去した。残渣をシリカゲルクロマトグラフィー【クロロホルム：メタノール=10:1の混合溶媒で溶出】に付し、1-ブチル-5-クロロ-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール1.2gを得た。次いで、フマル酸0.8gにエタノール10mlを加え、加熱溶解した。この溶液を1-ブチル-5-クロロ-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール1.2g中に加えた。冷後析出した結晶をろ取し、得られた結晶を酢酸エチル-エタノールの混合溶媒から再結晶し、標記化合物0.9gを得た。

【0058】mp 167.0-169.0°C

NMR(CDCl₃-DMSO-d₆, δ ppm): 0.58-2.10(7H,m), 2.45(3H,s), 2.61-3.00(4H,m), 3.03-3.61(4H,m), 4.01(2H,t), 6.71(3H,s), 7.04-7.50(3H,m), 9.65(3H,brs).

元素分析値 (C₁₁H₁₄ClN₂·3/2C₂H₄Oとして) :

計算値 (%) C, 54.94; H, 6.08; N, 11.65

実測値 (%) C, 54.82; H, 5.90; N, 11.62

【0059】実施例6

1-ブチル-5-クロロ-2-(1-ビペラジニル)ベンズイミダゾロン：1-ブチル-5-クロロ-2-ベンズイミダゾロン（製造例1第2表中の化合物No.4参照）10.0gをオキシ塩化リン20ml中に1時間還流した。放冷後、反応混合物を氷水に注ぎ、クロロホルムで抽出した。クロロホルム層を水酸化ナトリウム水溶液、水で洗浄し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去して粗製の1-(2-ブチル)-2,5-ジクロロベンズイミダゾール23.0gを得た。次いで、得られた粗製の1-(2-ブチル)-2,5-ジクロロベンズイミダゾール17.0gとN-メチルビペラジン28.0gを混合し、140°Cで2.5時間攪拌した。反応混合物に水酸化ナトリウム水溶液を加え、クロロホルムで抽出した。クロロホルム層を水洗し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去することにより標記化合物16gを得た。この一部をシリカゲルクロマトグラフィー【クロロホルム：メタノール=10:1の混合溶媒で溶出】に付し、アセトニトリルから再結晶したもののは以下の物性値を示した。

【0060】mp 102.0-105.0°C

NMR(CDCl₃, δ ppm): 0.67-2.24(7H,m), 2.40(1H,s), 2.84-3.64(8H,m), 4.04(2H,t), 6.99-7.84(3H,m).

元素分析値 (C₁₁H₁₄ClN₂として) :

計算値 (%) C, 61.53; H, 7.23; N, 19.13

実測値 (%) C, 61.33; H, 7.35; N, 18.95

【0061】実施例7

5-クロロ-2-(4-メチル-1-ビペラジニル)-1-テトラヒドロフルフリルベンズイミダゾール：5-クロロ-1-エチル-2-ベンズイミダゾロンの替わりに5-クロロ-1-テトラヒドロフルフリル-2-ベンズイミダゾロン（製造例1第2表中の化合物No.5参照）を用いる他は実施例1と同様にして標記化合物を得た。（ただし、イソプロピルアルコールから再結晶した。）

【0062】mp 96.0-98.0°C

NMR(CDCl₃, δ ppm): 1.30-2.23(4H,m), 2.38(3H,s), 2.46-2.90(4H,m), 3.20-3.60(4H,m), 3.60-4.60(5H,m), 7.00-7.82(3H,m).

元素分析値 (C₁₁H₁₄ClN₂Oとして) :

計算値 (%) C, 60.98; H, 6.92; N, 16.73

実測値 (%) C, 60.87; H, 6.76; N, 16.80

【0063】実施例8

1-(2-ブチル)-5-クロロ-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール：1-(2-ブチル)-5-クロロ-2-ベンズイミダゾロン（製造例1第2表中の化合物No.6参照）23gをオキシ塩化リン23ml中に3時間還流した。放冷後、反応混合物を氷水に注ぎ、クロロホルムで抽出した。クロロホルム層を水酸化ナトリウム水溶液、水で洗浄し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去して粗製の1-(2-ブチル)-2,5-ジクロロベンズイミダゾール23.0gを得た。次いで、得られた粗製の1-(2-ブチル)-2,5-ジクロロベンズイミダゾール17.0gとN-メチルビペラジン28.0gを混合し、140°Cで2.5時間攪拌した。

反応混合物に水酸化ナトリウム水溶液を加え、クロロホルムで抽出した。クロロホルム層を水洗し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去することにより標記化合物16gを得た。この一部をシリカゲルクロマトグラフィー【クロロホルム：メタノール=10:1の混合溶媒で溶出】に付し、アセトニトリルから再結晶したもののは以下の物性値を示した。

【0064】mp 104.0-106.0°C

NMR(CDCl₃, δ ppm): 0.69(3H,t), 1.61(3H,d), 1.78-2.11(2H,m), 2.49(3H,s), 2.51-2.96(4H,m), 3.09-3.66(4H,m), 3.96-4.76(1H,m), 7.04-7.87(3H,m).

元素分析値 (C₁₁H₁₄ClN₂として) :

計算値 (%) C, 62.63; H, 7.56; N, 18.26

実測値 (%) C, 62.73; H, 7.70; N, 18.37

【0065】実施例9

5-クロロ-1-イソブチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール：1-(2-ブチル)-5-クロロ-2-ベンズイミダゾロンの替わりに5-クロロ-1-イソブチル-2-ベンズイミダゾロン（製造例1第2表中の化合物No.7参照）を用いる他は実施例8と同様にして反応後、シリカゲルクロマトグラフィー【クロロホルム：メタノール=20:1の混合溶媒で溶出】で精製することにより標記化合物を得た。

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[0066] mp 145.0-147.0°C

NMR(CDCl₃, δ ppm): 0.87(6H,d), 1.78-2.41(1H,m), 2.42(3H,s), 2.53-2.98(4H,m), 3.08-3.70(4H,m), 3.86(2H,d), 6.98-7.98(3H,m).

元素分析値 (C₁₁H₁₄N₂Oとして) :

計算値 (%) C, 62.63; H, 7.56; N, 18.26

実測値 (%) C, 62.61; H, 7.70; N, 18.26

[0067] 実施例 10

5-クロロ-2-(4-メチル-1-ビペラジニル)-1-(3-ペンチル)ベンズイミダゾール・1フマル酸塩: 1-(2-ブチル)-5-クロロ-2-ベンズイミダゾロンの替わりに5-クロロ-1-(3-ペンチル)-2-ベンズイミダゾロン(製造例1第2表中の化合物No.8参照)を用いる他は実施例8と同様にして5-クロロ-2-(4-メチル-1-ビペラジニル)-1-(3-ペンチル)ベンズイミダゾールを得た。次いで、実施例5と同様にしてフマル酸塩とし、エタノールから再結晶することにより標記化合物を得た。

[0068] mp 201.0-202.0°C

NMR(DMSO-d₆, δ ppm): 0.69(6H,t), 1.51-2.19(4H,m), 2.37(3H,s), 2.47-2.99(4H,m), 3.00-3.51(4H,m), 3.70-4.50(1H,m), 6.60(2H,s), 6.93-7.64(3H,m), 10.11(2H,brs).

元素分析値 (C₁₁H₁₄N₂·C₄H₄O₂として) :

計算値 (%) C, 57.73; H, 6.69; N, 12.82

実測値 (%) C, 57.54; H, 6.63; N, 12.76

[0069] 実施例 11

5-クロロ-1-シクロベンチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール: 1-(2-ブチル)-5-クロロ-2-ベンズイミダゾロンの替わりに5-クロロ-1-シクロベンチル-2-ベンズイミダゾロン(製造例1第2表中の化合物No.9参照)を用いる他は実施例8と同様にして反応後、アセトニトリルから再結晶することにより標記化合物を得た。

[0070] mp 168.0-171.0°C

NMR(CDCl₃, δ ppm): 1.26-2.36(8H,m), 2.38(3H,s), 2.49-2.93(4H,m), 3.07-3.64(4H,m), 4.26-5.26(1H,m), 6.96-7.86(3H,m).

元素分析値 (C₁₁H₁₄N₂として) :

計算値 (%) C, 64.04; H, 7.27; N, 17.57

実測値 (%) C, 64.00; H, 7.17; N, 17.75

[0071] 実施例 12

5-クロロ-1-(3-エトキシプロビル)-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール: 1-(2-ブチル)-5-クロロ-2-ベンズイミダゾロンの替わりに5-クロロ-1-(3-エトキシプロビル)-2-ベンズイミダゾロン(製造例1第2表中の化合物No.10参照)を用いる他は実施例8と同様にして反応後、ヘキサンから再結晶することにより標記化合物を得た。

[0072] mp 72.0-74.0°C

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NMR(CDCl₃, δ ppm): 1.21(3H,t), 1.72-2.24(2H,m), 2.38(3H,s), 2.49-2.82(4H,m), 3.20-3.79(8H,m), 4.15(2H,t), 7.04-7.82(3H,m).

元素分析値 (C₁₁H₁₄N₂O · 1/4H₂Oとして) :

計算値 (%) C, 59.81; H, 7.53; N, 16.41

実測値 (%) C, 59.84; H, 7.50; N, 16.47

[0073] 実施例 13

1-エチル-5-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール・2フマル酸塩: 1-(2-ブチル)-5-クロロ-2-ベンズイミダゾロンの替わりに1-エチル-5-メチル-2-ベンズイミダゾロン[Helv.Chim.Acta, 59(1), 148-155(1976) 参照]を用いる他は実施例8と同様にして1-エチル-5-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾールを得た。次いで、実施例5と同様にしてフマル酸塩とし、アセトニトリルから再結晶することにより標記化合物を得た。

[0074] mp 168.0-171.0°C

NMR(DMSO-d₆, δ ppm): 1.34(3H,t), 2.48(3H,s), 2.57(3H,s), 2.75-3.18(4H,m), 3.18-3.60(4H,m), 4.07(2H,q), 6.64(4H,s), 6.82-7.50(3H,m), 11.04(4H,brs).

元素分析値 (C₁₁H₁₄N₂ · 2C₄H₄O₂として) :

計算値 (%) C, 56.32; H, 6.16; N, 11.42

実測値 (%) C, 56.28; H, 6.03; N, 11.56

[0075] 実施例 14

1-ブチル-5-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール・3/2フマル酸塩: 1-(2-ブチル)-5-クロロ-2-ベンズイミダゾロンの替わりに1-ブチル-5-メチル-2-ベンズイミダゾロン(製造例1第2表中の化合物No.11参照)を用いる他は実施例8と同様にして1-ブチル-5-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾールを得た。次いで、実施例5と同様にしてフマル酸塩とし、エタノールから再結晶することにより標記化合物を得た。

[0076] mp 147.0-162.0°C

NMR(DMSO-d₆, δ ppm): 0.52-2.10(7H,m), 2.47(3H,s), 2.52(3H,s), 2.70-3.12(4H,m), 3.12-3.67(4H,m), 4.01(2H,t), 6.62(3H,s), 6.82-7.52(3H,m), 8.69(3H,brs).

元素分析値 (C₁₁H₁₄N₂ · 3/2C₄H₄O₂として) :

計算値 (%) C, 59.99; H, 7.00; N, 12.17

実測値 (%) C, 59.83; H, 6.80; N, 12.11

[0077] 実施例 15

1-イソブチル-5-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール: 1-(2-ブチル)-5-クロロ-2-ベンズイミダゾロンの替わりに1-イソブチル-5-メチル-2-ベンズイミダゾロン(製造例1第2表中の化合物No.12 参照)を用いる他は実施例8と同様にして反応後、シリカゲルクロマトグラ

50 フィー [クロロホルム: メタノール=10:1の混合浴媒で

溶出]に付し、次いで、ヘキサンから再結晶することにより標記化合物を得た。

[0078] mp 119.0-121.0°C

NMR(CDCl_3 , δ ppm): 0.85(6H, d), 1.90-2.38(1H, m), 2.38(3H, s), 2.44(3H, s), 2.50-2.90(4H, m), 3.10-3.60(4H, m), 3.80(2H, d), 6.80-7.60(3H, m).

元素分析値 ($\text{C}_8\text{H}_{14}\text{N}_2$ として)

計算値 (%) C, 71.29; H, 9.15; N, 19.56

実測値 (%) C, 71.29; H, 9.28; N, 19.73

[0079] 実施例 1 6

5-メチル-1-(3-エトキシプロピル)-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール・1

フマル酸塩: 1-(2-ブチル)-5-クロロ-2-ベンズイミダゾロンの替わりに 1-(3-エトキシプロピル)-5-メチル-2-ベンズイミダゾロン(製造例1第2表中の化合物No.13 参照)を用いる他は実施例8と同様にして反応後、シリカゲルクロマトグラフィー[クロロホルム:メタノール=10:1の混合溶媒で溶出]に付し、5-メチル-1-(3-エトキシプロピル)-2-(4-メチル-1-ビペラジニル)ベンズイミダゾールを得た。次いで、実施例5と同様にしてフマル酸塩とし、エタノールから再結晶することにより標記化合物を得た。

[0080] mp 149.0-150.0°C

NMR(DMSO-d_6 , δ ppm): 1.13(3H, t), 1.50-2.20(2H, m), 2.35(3H, s), 2.45-2.98(4H, m), 3.00-3.70(8H, m), 4.07(2H, t), 6.61(2H, s), 6.76-7.42(3H, m), 9.36(2H, brs).

元素分析値 ($\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}$ ・ $\text{C}_2\text{H}_4\text{O}_4$ ・ $3/4\text{H}_2\text{O}$ として)

計算値 (%) C, 59.24; H, 7.57; N, 12.56

実測値 (%) C, 59.37; H, 7.61; N, 12.66

[0081] 実施例 1 7

1-ブチル-5-フルオロ-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール・3/2 フマル酸塩: 1-(2-ブチル)-5-クロロ-2-ベンズイミダゾロンの替わりに 1-ブチル-5-フルオロ-2-ベンズイミダゾロン(製造例1第2表中の化合物No.14 参照)を用いる他は実施例8と同様にして反応後、シリカゲルクロマトグラフィー[クロロホルム:メタノール=13:1の混合溶媒で溶出]に付し、1-ブチル-5-フルオロ-2-(4-メチル-1-ビペラジニル)ベンズイミダゾールを得た。次いで、実施例5と同様にしてフマル酸塩とし、エタノールから再結晶することにより標記化合物を得た。

[0082] mp 170.0-172.0°C

NMR(DMSO-d_6 , δ ppm): 0.68-2.20(7H, m), 2.52(3H, s), 2.70-3.14(4H, m), 3.14-3.70(4H, m), 4.08(2H, t), 6.63(3H, s), 6.72-7.70(3H, m), 10.12(3H, brs).

元素分析値 ($\text{C}_{14}\text{H}_{18}\text{FN}_2$ ・ $3/2\text{C}_2\text{H}_4\text{O}_4$ として)

計算値 (%) C, 56.89; H, 6.29; N, 12.06

実測値 (%) C, 56.95; H, 6.17; N, 12.13

[0083] 実施例 1 8

5-クロロ-1-(2-エトキシエチル)-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール・2マレイン酸塩: 1-(2-ブチル)-5-クロロ-2-ベンズイミダゾロンの替わりに 5-クロロ-1-(2-エトキシエチル)-2-ベンズイミダゾロン(製造例1第2表中の化合物No.15 参照)を用いる他は実施例8と同様にして反応後、シリカゲルクロマトグラフィー[クロロホルム:メタノール=10:1の混合溶媒で溶出]に付し、5-クロロ-1-(2-エトキシエチル)-2-(4-メチル-1-ビペラジニル)ベンズイミダゾールを得た。次いで、フマル酸の替わりにマレイン酸を用いる他は実施例5と同様にしてマレイン酸塩とし、酢酸エチル-エタノールの混合溶媒から再結晶することにより標記化合物を得た。

mp 127.0-129.0°C

NMR(DMSO-d_6 , δ ppm): 1.00(3H, t), 2.89(3H, s), 3.04-3.95(12H, m), 4.24(2H, t), 6.15(4H, s), 6.91-7.62(3H, m), 1.40(4H, brs).

元素分析値 ($\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2 \cdot 2\text{C}_2\text{H}_4\text{O}_4$ として)

計算値 (%) C, 51.94; H, 5.63; N, 10.10

実測値 (%) C, 51.90; H, 5.79; N, 10.23

[0084] 実施例 1 9

1-シクロベンチル-5-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール: 1-(2-ブチル)-5-クロロ-2-ベンズイミダゾロンの替わりに 1-シクロベンチル-5-メチル-2-ベンズイミダゾロン(製造例1第2表中の化合物No.16 参照)を用いる他は実施例8と同様にして反応後、酢酸エチルから再結晶することにより標記化合物を得た。

[0085] mp 125.0-125.5°C

NMR(CDCl_3 , δ ppm): 1.30-2.30(8H, m), 2.36(3H, s), 2.43(3H, s), 2.49-2.95(4H, m), 3.07-3.62(4H, m), 4.27-5.17(1H, m), 6.77-7.67(3H, m).

元素分析値 ($\text{C}_{14}\text{H}_{18}\text{N}_2 \cdot 1/10\text{H}_2\text{O}$ として)

計算値 (%) C, 72.01; H, 8.80; N, 18.66

実測値 (%) C, 71.91; H, 8.79; N, 18.67

[0086] 実施例 2 0

6-アミノ-5-クロロ-1-エチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール: 5-クロロ-1-エチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール(実施例1参照)2.5gを酢酸4mLに溶解した。発煙硝酸3.8gを加えた後、60°Cで40分間攪拌した。反応混合物を氷水に注ぎ、2N水酸化ナトリウム溶液で中和し、クロロホルムで抽出した。有機層を水洗し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去し、5-クロロ-1-エチル-2-(4-メチル-1-ビペラジニル)-6-ニトロベンズイミダゾール2.8gを得た。次いで、得られた5-クロロ-1-エチ

ル-(4-メチル-1-ビペラジニル)-6-ニトロベ

ンズイミダゾール2.0gをエタノール15mlと濃塩酸4mlの混合溶媒に懸濁し、亜鉛末2.4gを少しずつ加え60°Cで30分間攪拌した。アンモニア水を加えてアルカリ性にし、酢酸エチルで抽出した。酢酸エチル層を水洗し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去した。残渣をシリカゲルクロマトグラフィー【クロロホルム：メタノール=10:1の混合溶媒で溶出】に付し、アセトニトリルから再結晶することにより標記化合物0.5gを得た。

【0087】mp 184.0-187.0°C

NMR(CDCl₃, δ ppm): 1.37(3H,t), 2.35(3H,s), 2.45-2.90(4H,m), 3.02-3.60(4H,m), 3.70-4.40(4H,m), 6.63(1H,s), 7.52(1H,s).

元素分析値(C₁₁H₁₄CIN₄として)：

計算値(%) C, 57.23; H, 6.86; N, 23.84

実測値(%) C, 57.36; H, 6.73; N, 23.82

以下、実施例20における5-クロロ-1-エチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾールの替わりに、前記実施例に記載の対応する化合物【一般式(I)の化合物のうちR₁が水素原子である対応化合物】を用いる他は実施例20と同様にして実施例21～36の各化合物を得た。ただし、実施例35は、更に実施例5と同様にしてフマル酸塩に導いた。

【0088】実施例21

6-アミノ-5-クロロ-1-シクロプロビル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール：

mp 205.0(分解)

NMR(CDCl₃, δ ppm): 0.94-1.47(4H,m), 2.39(3H,s), 2.47-2.83(4H,m), 2.83-3.27(1H,m), 3.27-3.73(4H,m), 3.98(2H,brs), 6.80(1H,s), 7.60(1H,s).

元素分析値(C₁₁H₁₄CIN₄として)：

計算値(%) C, 58.91; H, 6.59; N, 22.90

実測値(%) C, 58.83; H, 6.49; N, 23.01

【0089】実施例22

6-アミノ-5-クロロ-2-(4-メチル-1-ビペラジニル)-1-プロビルベンズイミダゾール：

mp 180.5-182.0°C

NMR(CDCl₃, δ ppm): 0.90(3H,t), 1.40-2.20(2H,m), 2.35(3H,s), 2.45-2.87(4H,m), 3.05-3.60(4H,m), 3.62-4.30(4H,m), 6.57(1H,s), 7.47(1H,s).

元素分析値(C₁₁H₁₄CIN₄として)：

計算値(%) C, 58.53; H, 7.20; N, 22.75

実測値(%) C, 58.45; H, 7.07; N, 22.73

【0090】実施例23

6-アミノ-5-クロロ-1-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール：

mp 181.0-183.0°C

NMR(CDCl₃, δ ppm): 2.34(3H,s), 2.44-2.81(4H,m), 3.07-3.40(4H,m), 3.44(3H,s), 3.95(2H,brs), 6.51(1H,s), 7.43

(1H,s).

元素分析値(C₁₁H₁₄CIN₄として)：

計算値(%) C, 55.81; H, 6.48; N, 25.03

実測値(%) C, 55.83; H, 6.40; N, 24.97

【0091】実施例24

6-アミノ-1-ブチル-5-クロロ-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール：

mp 160.0-164.0°C

10 NMR(CDCl₃, δ ppm): 0.66-2.16(7H,m), 2.37(3H,s), 2.46-2.80(4H,m), 3.14-3.55(4H,m), 3.61-4.56(4H,m), 6.65(1H,s), 7.54(1H,s).

元素分析値(C₁₁H₁₄CIN₄として)：

計算値(%) C, 59.71; H, 7.52; N, 21.76

実測値(%) C, 59.62; H, 7.41; N, 21.73

【0092】実施例25

6-アミノ-5-クロロ-2-(4-メチル-1-ビペラジニル)-1-(2-ブチル)ベンズイミダゾール：

mp 207.0-210.0°C

20 NMR(CDCl₃, δ ppm): 0.70(3H,t), 1.57(3H,d), 1.77-2.32(2H,m), 2.40(3H,s), 2.50-2.97(4H,m), 2.97-3.62(4H,m), 3.82-4.80(3H,m), 6.90(1H,s), 7.65(1H,s).

元素分析値(C₁₁H₁₄CIN₄として)：

計算値(%) C, 59.71; H, 7.52; N, 21.76

実測値(%) C, 59.73; H, 7.70; N, 21.75

【0093】実施例26

6-アミノ-5-クロロ-1-イソブチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール：

mp 157.0-159.0°C

30 NMR(CDCl₃, δ ppm): 0.84(6H,d), 1.62-2.33(1H,m), 2.38(3H,s), 2.48-2.92(4H,m), 3.02-3.60(4H,m), 3.60-4.52(4H,m), 6.67(1H,s), 7.60(1H,s).

元素分析値(C₁₁H₁₄CIN₄として)：

計算値(%) C, 59.71; H, 7.52; N, 21.76

実測値(%) C, 59.78; H, 7.69; N, 21.69

【0094】実施例27

6-アミノ-5-クロロ-2-(4-メチル-1-ビペラジニル)-1-(3-ベンチル)ベンズイミダゾール：

mp 220.0-221.0°C

40 NMR(CDCl₃, δ ppm): 0.76(6H,t), 1.50-2.29(4H,m), 2.35(3H,s), 2.47-2.90(4H,m), 3.00-3.45(4H,m), 3.60-4.50(3H,m), 6.74(1H,s), 7.51(1H,s).

元素分析値(C₁₁H₁₄CIN₄として)：

計算値(%) C, 60.79; H, 7.80; N, 20.85

実測値(%) C, 60.86; H, 7.95; N, 20.99

【0095】実施例28

6-アミノ-5-クロロ-1-シクロベンチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール：

mp 220.5-222.5°C

50 NMR(CDCl₃, δ ppm): 1.43-2.30(8H,m), 2.36(3H,s), 2.46-

27

2.93(4H,m), 3.10-3.55(4H,m), 3.87(2H,brs), 4.30-5.13
(1H,m), 6.65(1H,s), 7.49(1H,s).

元素分析値 (C₁, H₆, ClN₂として) :

計算値 (%) C, 61.16; H, 7.25; N, 20.98

実測値 (%) C, 61.06; H, 7.08; N, 21.15

[0096] 実施例29

6-アミノ-5-クロロ-1-(3-エトキシプロピル)-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール:

mp 119.0-120.0°C

NMR(CDCl₃, δ ppm): 1.26(3H,t), 1.74-2.34(2H,m), 2.42
(3H,s), 2.51-2.95(4H,m), 3.10-3.82(8H,m), 3.82-4.44(4
H,m), 6.85(1H,s), 7.71(1H,s).

元素分析値 (C₁, H₆, ClN₂Oとして) :

計算値 (%) C, 58.03; H, 7.45; N, 19.90

実測値 (%) C, 57.92; H, 7.56; N, 19.81

[0097] 実施例30

6-アミノ-5-クロロ-2-(4-メチル-1-ビペラジニル)-1-テトラヒドロフルフリルベンズイミダゾール:

mp 163.0-165.0°C

NMR(CDCl₃, δ ppm): 1.50-2.19(4H,m), 2.33(3H,s), 2.42-
2.80(4H,m), 3.07-3.40(4H,m), 3.50-4.50(7H,m), 6.75(1
H,s), 7.49(1H,s).

元素分析値 (C₁, H₆, ClN₂Oとして) :

計算値 (%) C, 58.36; H, 6.91; N, 20.02

実測値 (%) C, 58.20; H, 6.88; N, 20.06

[0098] 実施例31

6-アミノ-1-エチル-5-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール:

mp 148.0-153.0°C (エタノールから再結晶)

NMR(CDCl₃, δ ppm): 1.36(3H,t), 2.22(3H,s), 2.33(3H,
s), 2.46-3.00(4H,m), 3.10-3.45(4H,m), 3.60(2H,brs), 3.
96(2H,q), 6.60(1H,s), 7.37(1H,s).

元素分析値 (C₁, H₆, N, · 1/4H₂Oとして) :

計算値 (%) C, 64.83; H, 8.52; N, 25.20

実測値 (%) C, 64.91; H, 8.63; N, 25.24

[0099] 実施例32

6-アミノ-1-ブチル-5-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール:

mp 155.0-158.0°C

NMR(CDCl₃, δ ppm): 0.60-2.10(7H,m), 2.25(3H,s), 2.37
(3H,s), 2.48-3.07(4H,m), 3.07-3.45(4H,m), 3.60(2H,br
s), 3.90(2H,t), 6.52(1H,s), 7.33(1H,s).

元素分析値 (C₁, H₆, N, Fとして) :

計算値 (%) C, 67.74; H, 9.03; N, 23.23

実測値 (%) C, 67.88; H, 9.21; N, 23.18

[0100] 実施例33

6-アミノ-1-イソブチル-5-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール:

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mp 122.0-124.0°C (イソプロピルアルコールから再結晶)

NMR(CDCl₃, δ ppm): 0.83(6H,d), 1.47-2.17(1H,m), 2.22
(3H,s), 2.34(3H,s), 2.43-2.87(4H,m), 2.97-3.38(4H,m),
3.47(2H,brs), 3.71(2H,d), 6.53(1H,s), 7.32(1H,s).

元素分析値 (C₁, H₆, N, Fとして) :

計算値 (%) C, 67.74; H, 9.03; N, 23.23

実測値 (%) C, 67.62; H, 9.22; N, 23.02

[0101] 実施例34

6-アミノ-1-シクロヘンチル-5-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール:

mp 194.0-196.0°C (ジオキサン-ヘキサンの混合溶媒から再結晶)

NMR(CDCl₃, δ ppm): 1.38-2.20(8H,m), 2.24(3H,s), 2.36
(3H,s), 2.48-2.98(4H,m), 2.98-3.38(4H,m), 3.50(2H,br
s), 4.23-5.18(1H,m), 6.66(1H,s), 7.27(1H,s).

元素分析値 (C₁, H₆, N, Fとして) :

計算値 (%) C, 68.97; H, 8.68; N, 22.34

実測値 (%) C, 68.90; H, 8.76; N, 22.46

[0102] 実施例35

6-アミノ-1-(3-エトキシプロピル)-5-メチル-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール·1フマル酸塩:

mp 198.0-199.0°C (分解) (エタノールから再結晶)

NMR(DMSO-d₆, δ ppm): 1.12(3H,t), 1.46-1.98(2H,m), 2.1
1(3H,s), 2.40(3H,s), 2.56-2.96(4H,m), 2.96-3.66(8H,
m), 3.91(2H,t), 6.53(3H,s), 6.69-7.30(5H,m).

元素分析値 (C₁, H₆, N, O-C₂H₄O, · 1/2H₂Oとして) :

計算値 (%) C, 57.88; H, 7.51; N, 15.34

実測値 (%) C, 57.87; H, 7.30; N, 15.36

[0103] 実施例36

6-アミノ-1-ブチル-5-フルオロー-2-(4-メチル-1-ビペラジニル)ベンズイミダゾール:

mp 124.5-125.0°C

NMR(CDCl₃, δ ppm): 0.47-2.17(7H,m), 2.35(3H,s), 2.44-
2.85(4H,m), 2.85-3.57(4H,m), 3.57-4.57(4H,m), 6.60(1
H,d), 7.15(1H,d).

元素分析値 (C₁, H₆, N, Fとして) :

計算値 (%) C, 62.93; H, 7.92; N, 22.93

実測値 (%) C, 62.86; H, 7.71; N, 22.86

[0104] 実施例37

6-アミノ-2-(4-アミノ-1-ビペラジニル)-5-クロロ-1-イソプロピルベンズイミダゾール:

(1) 5-クロロ-1-イソプロピル-6-ニトロ-2-(1-ビペラジニル)ベンズイミダゾール (製造例2
参照) 0.32g を4N塩酸3ml 中に懸濁し、亜硝酸ナトリウム
0.07g を加え60°Cで1時間攪拌した。反応混合物を酢酸エチルで洗浄し、水層を水酸化ナトリウム水溶液でア
ルカリ性として酢酸エチルで抽出した。有機層を水洗

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し、無水硫酸マグネシウムで乾燥後、溶媒を減圧下に留去した。残渣をシリカゲルクロマトグラフィー【クロロホルム：メタノール=10:1の混合溶媒で溶出】に付し、5-クロロ-1-イソプロピル-6-ニトロ-2-(4-ニトロソ-1-ビペラジニル)ベンズイミダゾール0.03gを得た。なお、この一部をとってジメチルホルムアミドから再結晶したものは以下の物性値を示した。

[0105] mp 216.0-218.0°C

NMR(DMSO-d₆, δ ppm): 1.61(6H,d), 3.04-3.78(4H,m), 3.78-4.24(2H,m), 4.24-5.14(3H,m), 7.68(1H,s), 8.30(1H,s).

元素分析値(C₁₁H₁₀N₂Oとして) :

計算値(%) C, 52.09; H, 5.93; N, 26.04

実測値(%) C, 52.24; H, 5.89; N, 25.91

[0106] (2) 5-クロロ-1-イソプロピル-6-ニトロ-2-(4-ニトロソ-1-ビペラジニル)ベンズイダゾール2.6gをエタノール24ml中に加え、濃塩酸6mlを加えた。次いで亜鉛末3.0gを加えた後60°Cで6分間攪拌した。水酸化ナトリウム水溶液を加えてアルカリ性にし、クロロホルムで抽出した。クロロホルム層を水洗し、無水硫酸マグネシウムで乾燥後、溶媒を減圧下に留去した。残渣をシリカゲルクロマトグラフィー【クロロホルム：メタノール=50:1の混合溶媒で溶出】に付し、6-アミノ-5-クロロ-1-イソプロピル-2-(4-ニトロソ-1-ビペラジニル)ベンズイミダゾー

ル0.8gを得た。なお、この一部をとって酢酸エチルから再結晶したものは以下の物性値を示した。

[0107] mp 172.0-174.0°C

NMR(CDCl₃, δ ppm): 1.82(6H,d), 2.72-5.32(11H,m), 7.09(1H,s), 7.76(1H,s).

元素分析値(C₁₁H₁₀N₂Oとして) :

計算値(%) C, 52.09; H, 5.93; N, 26.04

実測値(%) C, 52.24; H, 5.89; N, 25.91

[0108] (3) 6-アミノ-5-クロロ-1-イソプロピル-2-(4-ニトロソ-1-ビペラジニル)ベンズイミダゾール0.4gを酢酸10ml中に溶解し、亜鉛末0.5gを加え60°Cで10分間攪拌した。水酸化ナトリウム水溶液を加え、クロロホルムで抽出した。有機層を水洗し、無水硫酸マグネシウムで乾燥した後、溶媒を減圧下に留去した。残渣をシリカゲルクロマトグラフィー【クロロホルム：メタノール=10:1の混合溶媒で溶出】に付し、6-アミノ-2-(4-アミノ-1-ビペラジニル)-5-クロロ-1-イソプロピルベンズイミダゾール0.17gを得た。

[0109] mp 175.0-179.0°C

NMR(CDCl₃, δ ppm): 1.53(6H,d), 2.60-3.11(4H,m), 3.11-4.70(8H,m), 4.70-5.00(1H,m), 6.81(1H,s), 7.49(1H,s).

元素分析値(C₁₁H₁₀N₄として) :

計算値(%) C, 54.45; H, 6.85; N, 27.21

実測値(%) C, 54.66; H, 6.77; N, 27.07